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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/564,458
Filing Date: January 12, 2006
Appellant(s): ANDERSON ET AL.

Sheldon Heber
For Appellant

EXAMINER'S ANSWER

This is in response to Appellant's brief on appeal filed 07/23/2010.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The Examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claim

The following is a list of claims that are rejected and pending in the application.

Claims 1, 4, 5, 6-9, 33-36 and 38-54 are pending.

Claims 1, 4, 7-9, 33-35 and 38-54 are rejected.

Claims 5, 6 and 36 are objected to.

Claims 2, 3, 10-32 and 37 are canceled.

(4) Status of Amendment After-Final

The examiner has no comment on the Appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the appeal brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the Appellants' statement on the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office Action from which the appeal is taken (as modified by

any advisory actions) is being maintained by the examiner. No new grounds of rejection are provided.

(7) Non-appealable Issue

The brief presents arguments relating to certain claims that are objected to. This issue relates to petitionable subject matter under 37 CFR 1.181 and not to appealable subject matter. See MPEP § 1002 and § 1201.

(8) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the Appellant's brief.

(9) Evidence Relied Upon

The following evidence is relied upon by the Office in rejecting the appealed claims.

The following prior art references have been applied in the rejections.

1) McGuiness *et al. Mol. Microbiol.* 7: 505-514, February 1993

2) McGuiness *et al. Lancet* 337: 514-517, March 1991

3) Colman PM. *Research Immunol*. 145: 33-36, 1994

4) von Eiff *et. al. Diagn. Microbiol. Infect. Dis.* 58:297-302, 2007

5) US patent 6,841,154 issued to Foster *et al*. and published 01/11/2005.

(10) Grounds of Rejections

The following grounds of rejections are applicable to the appealed claims.

35 U.S.C. § 112, First Paragraph Rejection, Written Description

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

(A) Claims 1, 4, 7-9, 33-35, 38-44 and 49-51 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The elected polypeptide species examined in the instant application is SEQ ID NO: 1. The purified polypeptide immunogen claimed in the independent claim 1(b) and recited in the independent claim 8(b) is minimally required to (A) *consist* of a *fragment* of an amino acid sequence 94% identical to SEQ ID NO: 3, wherein the *fragment* comprises an amino acid sequence 94% identical to SEQ ID NO: 1, i.e., 6% non-identical, (i.e., polypeptide immunogen fragment variant); and (B) provide protective immune response against *S. aureus.* The generic limitation 'protective immune response against *S. aureus*' in claim 1 does not specify to whom the protective immune response is provided. The immunogen claimed in the independent claim 7 is minimally required to (A) consist of an amino acid sequence 90% identical to SEQ ID NO: 1, i.e., 10% non-identical, (i.e., immunogen variant) and one or more additional regions covalently joined thereto either at the carboxyl or the amino terminus as recited therein; and (B) provide protective immune response against *S. aureus.* The polypeptide immunogen of claim 7 is not required to be isolated or purified

and it *consists of* an amino acid sequence at least 90% identical to SEQ ID NO: 1 and one or more additional regions or moieties covalently joined to said sequence either at the carboxyl or the amino terminus, wherein each of the regions or the moieties is independently selected from a region or moiety having at least one of the following properties: enhancement of immune response, facilitation of purification, or facilitation of polypeptide stability. Although claim 7 does not include the recitation of providing 'protective immune response against *S. aureus*', the limitation 'immunogen' as defined at line 25 of page 2 of the specification, is required to have the ability to provide protective immunity, consistent with the intended prophylactic (i.e., vaccine) applications. The one or more additional regions or moieties as recited in claim 7 do not exclude the additional region or moiety sequences from an ORF0657n related polypeptide of any microbial source, but encompass such sequences. The polypeptide immunogen fragment claimed in the dependent claim 4 consists of an amino acid sequence at least 94% identical to SEQ ID NO: 1 (i.e., polypeptide immunogen fragment variant). Each of these polypeptide immunogen fragment variants is **required** to provide protective immunity against homologous or heterologous *S. aureus* in a human or non-human host. The polypeptide immunogen claimed in the dependent claims 33-35, 39-44 and 49-51 encompass further variants that differ from SEQ ID NO: 1 by up to 5-25 amino acid alterations. Note that the limitation 'amino acid alterations' encompasses amino acid deletions, substitutions, insertions and modifications. While these further variants claimed in claims 33-35 and 39-44 and carrying the recited additional amino acid alterations are required to

provide protective immunity against any strain of *S. aureus,* the further variants claimed in claims 49-51 and carrying the recited additional amino acid alterations are required to remain as immunogens. Again, the term 'immunogen' is defined at line 25 of page 2 of the specification as one having the ability to provide protective immunity. The limitation 'patient' in claim 8 and the limitation 'human' in claims 38, 40, 42 and 44 encompass immunosufficient, immunodeficient and immunocompromised human patients. Note that *S. aureus* encompasses homologous or heterologous strains of *S. aureus*, coagulase-positive and coagulase-negative *S. aureus*; multiple drug-resistant and methicillin-resistant strains of *S. aureus* (MRSA), various phage types of *S. aureus*, enterotoxigenic and non-enterotoxigenic *S. aureus,* and various other serotypes including non-typeable *S. aureus*. For instance, von Eiff *et al*. (*Diagn. Microbiol. Infect. Dis*. 58: 297-302, 2007, of record) teach the prevalence of clinical isolates of *S. aureus* as various *spa* serotypes and capsular serotypes. See abstract of von Eiff *et al*.

The claims thus encompass a vast genus of polypeptide immunogen variants that are fragment variants of SEQ ID NO: 3 which are further variants of SEQ ID NO: 1, having up to 6% non-identity to SEQ ID NO: 3 and SEQ ID NO: 1 (claims 1 and 8), and immunogen variants with up to 10% non-identity to SEQ ID NO: 1 (claim 7), each having the requisite ability to provide protective immunity against *S. aureus*. Any amino acids may be substituted, modified, or deleted along the length of SEQ ID NO: 3 and/or SEQ ID NO: 1 as long as the polypeptide fragment retains the percent identity as recited. The specification intends prophylactic applications for the claimed immunogen variants.

The *Written Description Guidelines* state:

> There is an inverse correlation between the level of predictability in the art and the amount of disclosure necessary to satisfy the written description requirement. For example, if there is a well-established correlation between the structure and function in the art, one skilled in the art will be able to reasonably predict the complete structure of the claimed invention from its function.

In *Enzo Biochem. Inc. v. Gen-Probe Inc.*, 323 F3.d 956, 964, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002), the Federal Circuit adopted a portion of the Guidelines proffered by the United States Patent and Trademark Office (USPTO). The court stated that:

> The written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics .. e.g., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

Enzo Biochem, 323 F.3d at p64, 63 USPQ2d at 1613 (citing Guidelines for Examination of Patent Applications under the 35 U.S.C § 112, first paragraph Written Description Requirement, 66 Fed. Requirement 1099, 1106 (January 5, 2001)). Sufficient description to show possession of a genus may be achieved by means of recitation of a representative number of polypeptides, defined by amino acid sequences falling within the scope of the genus, or recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. Possession may *not* be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features. See *University of Rochester*, 358 F.3d at 927, 69 USPQ2d at 1895.

The full-length COL ORF0657n polypeptide was known in the art at the time of the invention as taught by Foster *et al*. (US 6,841,154).

Appellants have acknowledged that the full-length ORF0657n sequence is *excluded* from the claimed invention. For example, at third full paragraph on page 9 of the amendment/remarks filed 08/18/08, Applicants stated the following [Emphasis added]:

> 'Claim 1 **excludes** SEQ ID NO: 2'.

Again, at first full paragraph on page 20 of Applicants' amendment/remarks filed 03/13/09, Applicants stated the following [Emphasis added]:

> Claims 1, 5, 7, and 8 were amended as discussed above, so that **the full-length ORF0657n sequence is not covered**. Claims 3, 4, 6, 7, 33-35, and 37-44 as previously presented provided for less than the full-length sequence.

Thus, by Applellants' own admission, SEQ ID NO: 2 is not covered by claims 1, 7 and 8. The SEQ ID NO: 28 is the *full-length* SEQ ID NO: 2 modified to contain additional amino acids at the amino terminus and at the carboxyl terminus. Accordingly, since SEQ ID NO: 2 is excluded from the instant claims, SEQ ID NO: 28 of the instant specification, which is longer than SEQ ID NO: 2, is also excluded from claims 1, 5 and 8 as well as claim 7. As Applicants have acknowledged, the ORF0657nI region of SEQ ID NO: 1 that overlaps with a portion of SEQ ID NO: 28 is 78% of SEQ ID NO: 28. See second paragraph on page 11 of Applicants' amendment/remarks filed 02/24/2010. Furthermore, SEQ ID NO: 28, SEQ ID NO: 2, and the sequences depicted in Figure 2A-2E are *not* a fragment of a polypeptide immunogen consisting of SEQ ID NO: 3 or a fragment of a 94% identical variant of SEQ ID NO: 3, and therefore do not fall within the scope of claims 1(b) and 8(b). SEQ ID NO: 28 and SEQ ID NO: 2 are excluded from claim 7 as well. The SEQ ID NO: 4 and SEQ ID NO: 5

polypeptide immunogen species are not 94% or 90% identical variants of SEQ ID NO: 1. SEQ ID NO: 3 is not a fragment of SEQ ID NO: 3 as required by claims 1(b) and 8(b). The SEQ ID NO: 3 polypeptide species is not a 94% or 90% identical variant of SEQ ID NO: 1. SEQ ID NO: 3 differs from SEQ ID NO: 1 by having more than 20 amino acid additions at the carboxyl terminus of a polypeptide consisting of an amino acid sequence 100% identical to SEQ ID NO: 1. SEQ ID NO: 4 differs from SEQ ID NO: 1 by having more than 20 amino acid additions at the carboxyl terminus of a polypeptide consisting of an amino acid sequence 99.8% identical to SEQ ID NO: 1. Furthermore, the ORF0657nI-equivalent region of SEQ ID NO: 2 or SEQ ID NO: 28 does not constitute a 90% or 94% identical variant species of SEQ ID NO: 1. Figures 4A-4H pertain to SEQ ID NO: 28, which sequence is acknowledged by Applicants as corresponding to the full length SEQ ID NO: 2 with a His-Tag and as being excluded from the scope of the claims. SEQ ID NO: 28 and the full length proteins depicted in Figures 2A-2E do not fall within the scope of the huge genus of variants currently claimed.

In the instant application, Applicants have shown possession of a purified polypeptide immunogen consisting of SEQ ID NO: 1, which is a truncated full length ORF0657n polypeptide (e.g., SEQ ID NO. 2) of *S. aureus* COL. See pages 5 and 8 of the specification. SEQ ID NO: 1 appears to consist of amino acids 42-486 of SEQ ID NO: 3. Figure 1A is said to depict polypeptides that were tested and found to be protective (shown by filled rectangles) and polypeptides tested and found **not** to be protective (shown by open rectangles). Of these, ORF0657nI species

(SEQ ID NO: 1) falling within the scope of the instant claims is said to be protective, although the strain of *S. aureus* used and the precise test used for protection is not disclosed. However, this single species is not representative of the huge genus of the claimed polypeptide immunogen variants, each consisting of an amino acid sequence that is up to 10% non-identical with SEQ ID NO: 1. This is critically important because the polypeptide depicted as fragment 2 in Figure 1A via one of the open rectangles *consists* of amino acids 82-486 of SEQ ID NO: 1 and therefore serves as a polypeptide consisting of an amino acid sequence that is 90.58% identical to SEQ ID NO: 1. This polypeptide variant was tested for protection and was found **not** to be protective. See first full paragraph on page 5 of the instant specification. This showing is indicative of the unpredictability in obtaining a polypeptide species that is about 10% non-identical in structure to SEQ ID NO: 1 and that concurrently remains protective against *S. aureus* infection. Furthermore, the instant specification at third full paragraph of page 8 also states that a fragment of SEQ ID NO: 2 consisting of amino acids 82-486 or amino acids 42-196 was **not** protective. Since the amino acid residues 42-486 of SEQ ID NO: 2 constitute SEQ ID NO 1, a fragment consisting of the amino acids 82-486 of SEQ ID NO: 2 becomes a fragment of SEQ ID NO: 3 with 91% sequence identity to SEQ ID NO: 1. Such a polypeptide fragment falling within the scope of the instant claim 7 is expressly disclosed as being **not** protective at third full paragraph of page 8 of the instant specification. This admitted non-protection by the fragments of SEQ ID NO: 2, 3 or 1 *consisting* of amino acids 82-486 or amino acids 42-196 indicates the

absence of one or more protective epitopes in these regions which span the whole length of SEQ ID NO. 1. Thus, *the unmodified SEQ ID NO: 1 when merely split into a fragment of amino acids 82-486, or a fragment of amino acids 42-196, looses its protective capacity*. This showing is indicative of the criticality of retaining all the amino acid residues of SEQ ID NO: 1 intact within the claimed fragment in order to retain the *requisite* function of providing protective immunity against *S. aureus*. Thus, not only is there a lack of structure-function correlation for a representative number of claimed polypeptide immunogen variant species within the instant specification, there is also a lack of predictability as to whether polypeptide variants having up to 10% non-identity to SEQ ID NO: 1 anywhere along SEQ ID NO: 1 would remain immunospecific to *S. aureus* and therefore provide protective immunity against *S. aureus* in a human or a non-human host. Without a convincing correlation between structure and function, the claims do little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. *Ex parte Kubin*, 83 USPQ2d 1410 (Bd. Pat. Appl. & Int. 2007) citing *Eli Lilly*, 119 F.3d at 1568, 43 USPQ at 1406 ('definition by function ….. does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is'). The specification does not disclose the precise structure of a representative number of polypeptide immunogen variants in which an amino acid sequence *consisting* of SEQ ID NO: 1 is varied to contain up to 25 amino acid alterations, or that are 90% or 94% identical to said SEQ ID NO: 1, wherein the polypeptide variants have the recited *requisite* protection function against *S. aureus*. The instant specification

does not disclose which up to 25 amino acid residues within SEQ ID NO: 1, or which up to 10% or 6% of amino acid residues within SEQ ID NO: 1, should be altered such that one can maintain the required biological function, i.e., the capacity to provide the requisite protective immunity against *S. aureus.* No other amino acid sequences of purified, isolated, or non-isolated polypeptide immunogen variants having up to 5-25 amino acid residues within a polypeptide *consisting* of SEQ ID NO: 1 altered, or having 10% or 6% of amino acid residues within SEQ ID NO: 1 varied, are described, wherein the resultant polypeptide variants are capable of *providing protective immunity* against homologous or heterologous strain, serotype, phage type, *Spa* type, or capsular type of *S. aureus* in a human or non-human host or patient. Clearly, there is lack of adequate description. It should be noted that written description requires more than a mere statement that something is a part of the invention. Applicants have not described what domains, contiguous or discontiguous antigenic determinants, or conformational or non-conformational epitopes of the recited polypeptide immunogen fragment variant are correlated with the required capacity to provide protective immunity against homologous or heterologous *S. aureus.*

With respect to the written description requirement, while 'examples explicitly covering the full scope of the claim language' typically will not be required, a sufficient number of representative species must be included 'to demonstrate that the patentee possesses the full scope of the [claimed] invention'. *Lizardtech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1345, 76 USPQ2d 1724, 1732 (Fed. Cir. 2005). In the instant case,

Applicants' specification does not contain a written description sufficient to show they had possession of the full scope of their claimed invention at the time the application was filed. The instant specification mentions of 'a polypeptide consisting of an amino acid sequence at least 90% identical to SEQ ID NO: 3 or a fragment thereof comprising an amino acid sequence structurally related to SEQ ID NO: 1'. However, the specification does not disclose a **correlation** between the function (i.e., capacity to provide protective immunity against homologous or heterologous strain, serotype, phage type, *Spa* type, **or** capsular type of *S. aureus*) and the precise structure, or conformational or non-conformational epitope(s) responsible for providing such protective immunity such that a skilled artisan would have known what alterations including deletions, substitutions, additions, or other variations could be made of the large number of alterations currently encompassed within the scope of the instant claims without losing the protective function. The specification does not adequately describe or identify the *S. aureus*-specific, or *S. aureus* serotype-specific, non-serotype-specific or *S. aureus* strain-specific linear or conformational protective epitopes within a polypeptide *consisting* of SEQ ID NO: 1 or within said amino acid sequence with up to 25 amino acid alterations therein, or within an amino acid sequence at least 90% identical to SEQ ID NO: 1. This description is important because for a polypeptide to be protective against *S. aureus*, it has to minimally bind immunospecifically with the corresponding native *S. aureus* polypeptide-specific antibody. A change of even a single amino acid residue is known to alter the folding of a polypeptide such that the antibody-binding region no longer recognizes

the polypeptide. See right column on page 33 of Colman PM. *Research Immunol*. 145: 33-36, 1994, of record. The instant specification at second full paragraph of page 12 describes that substituting-amino acids have similar properties such as amino acid size, charge, polarity, and hydrophobicity. However, it is recognized in the art that even a very conservative substitution may abolish binding. See first full paragraph on page 35 of Colman. Colman further taught that binding interactions could be considered less tolerant because the changes involved occur in what might be called the active site. See third full paragraph on page 35 of Colman. Although a microbial polypeptide having up to 25 amino acid alterations, or at least 10% or 6% non-identity with the native polypeptide, is expected in the art to generally induce some antibodies, the capacity of such antibodies to provide specific protective immunity against homologous or heterologous strain, serotype, phage type or capsular type of *S. aureus* in a human or non-human subject or patient is not predictable. The art reflects unpredictability as to which amino acids in a specific protein can be varied, i.e., replaced or added, without adversely affecting the functional properties of that specific protein. In other words, the retention of the immunospecificity following one or more amino acid substitutions, including conservative amino acid substitutions within a bacterial polypeptide, is not predictable. For instance, McGuinness *et al*. (*Mol. Microbiol*. 7: 505-514, Feb 1993, of record) taught that "[a] single amino acid change within an epitope, or an amino acid deletion outside an epitope, were both associated with loss of subtype specificity resulting from a change in the predicted conformation at the apex of the loop structure" in

case of a meningococcal polypeptide. See abstract. Similarly, McGuinness *et al*. (*Lancet* 337: 514-517, March 1991, of record) taught that a point mutation generating a single amino acid change in a P1.16-specific epitope in the VR2 region of the *porA* gene of a strain of *Neisseria meningitidis* of subtype P1.7,16 resulted in "striking changes in the structural and immunological properties of the class 1 protein" of this isolate. See abstract and page 514 of McGuinness *et al*. Thus, the state of the art at the time of the invention documented unpredictability in obtaining a functional variant of a microbial polypeptide that retains its specific immunological binding function(s). In the instant case, the purified polypeptide species *consisting* of SEQ ID NO: 1 appears to be a novel polypeptide of *S. aureus* and found to be protective against an undisclosed strain of *S. aureus.* See Figure 1A. However, Applicants did not describe the invention of the instant claims sufficiently to show that they had possession of the claimed genus of polypeptide immunogen or immunogen variants with up to 6% or 10% non-identity to SEQ ID NO: 1. See e.g., *Noelle v. Lederman*, 355 F.3d 1343, 1348, 69 USPQ2d 1508, 1513 (Fed. Cir. 2004) ('invention is, for purposes of the written description inquiry, *whatever is now claimed*'). Applicants should note that written description requires more than a mere statement that something is a part of the invention and a reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd*., 18 USPQ2d 1016. The instant claims are viewed as not meeting the written description provision of 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

(B) Claims 7-9 and 38-54 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 7, as amended, is vague and indefinite in the limitation: 'facilitates polypeptide stability', because it is unclear the stability of which polypeptide is being facilitated by the one or more additional regions or moieties. Does it mean that the claimed immunogen is unpurified and exists in association with a polypeptide, the stability of which polypeptide is facilitated by the one or more additional regions or moieties? The claim has no earlier recitation of any 'polypeptide' and therefore it is unclear the stability of which polypeptide is facilitated. The relationship, if any, of the polypeptide whose stability is facilitated to the claimed immunogen is not understood.

(b) Claim 8, as amended, is vague and indefinite in the broadening limitation: 'provides protective immunity against *S. aureus*' in line 3. The earlier part of the claim includes a narrower limitation reciting that the composition is to induce a protective immune response against *S. aureus* 'in a patient'. The earlier narrower limitation 'composition *able to induce a protective immune response against S. aureus in a patient'* comprising an *immunologically effective amount of* a purified polypeptide immunogen, is presented with the latter broader limitation '*that provides protective*

immunity against S. aureus', which renders the claim indefinite. The latter limitation 'provides protective immunity against *S. aureus'* does not specify that the protective immunity provided against *S. aureus* is --in said patient--, and therefore encompasses protective immunity provided against *S. aureus* in a non-patient, or a patient other than the one recited in line 2 of the claim. Is the protective immunity against *S. aureus* that is recited in line 3 of the claim provided to a subject other than 'a patient' recited in line 2, or to the same patient recited in line 2 of the claim?

(c) Claims 9 and 38-54, which depend directly or indirectly from claim 7 or 8, are also rejected as being indefinite, because of the indefiniteness identified above in the base claim.

(11) Response to Appellants' Arguments

(I) In response to the rejection of claims 1, 4, 7-9, 33-35, 38-44 and 49-51 made in paragraph 23 of the Office Action mailed 11/24/09 and maintained in paragraph 15 of the Office Action mailed 03/25/10 under 35 U.S.C § 112, first paragraph, as containing inadequate written description, Appellants argue the claims separately in different groups based on the sequence identity or number of alterations, as follows: (A) claims 1, 8, 9, and 38; (B) claim 4; (C) claims 33, 39, 40, and 49; (D) claims 34, 41, 42, and 50; (E) claims 35, 43, 44, and 51; and (F) claim 7.

Appellants submit the following arguments.

The test for written description sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art the inventor possessed the claimed subject matter as of the filing date. *Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.,* 598 F.3d 1336, 1351, 94

USPQ2d 1161, 1172 (Fed. Cir. Mar. 22, 2010) (citing *Vas-Cath Inc. v. Makurkar* 935 F.2d. 1555, 1562-1563, [19 USPQ2d 1111, 1117] (Fed. Cir. 1991). Written description of a genus requires a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus. *University of California v. Eli Lilly & Co.,* 119 F.3d 1559, 1568-1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The written description requirement can be satisfied by showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, *i.e.,* complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure,* or some combination of such characteristics. *Enzo Biochem, Inc. v. Gen-Probe Inc.,* 323 F.3d 956, 964, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002), citing to and discussing Patent Office Written Description Guidelines provided in 66 Fed. Reg. 1099, 1106 (January 5, 2001).

The present application conveys to those skilled in the art the inventors had possession of the claimed subject matter as of the filing date by providing representative species of polypeptides within the claimed genus. Representative species of polypeptides are illustrated by the use of SEQ ID NO: 1, and longer-length polypeptides containing a SEQ ID NO 1 region, to provide protection against heterologous challenge strains of S. *aureus.* The 'challenge strain' is the *S. aureus* used to infect a host. The heterologous challenge experiments described in the application involved a *S. aureus* challenge strain having a different ORF0657n region than the

corresponding region present in the protective immunogen. The ability of a polypeptide to provide protection against a heterologous strain of *S. aureus* demonstrates that alterations can be made to SEQ ID NO: 1 where protection is maintained and provides a strong expectation that the corresponding region from the challenge strain could also provide protection. For example, the ORF0657nl region from the challenge strain could be used to provide homologous protection, where the protective polypeptide has the same ORF0657nl region as the challenge strain. Examples of corresponding sequences from other strains of *S. aureus* are provided in the application in Figures 2A to 2E. The data provided with different polypeptides illustrate that the claimed genus is reasonably related to the provided structural descriptions, provides evidence that other species described in the application are protective, and supports further variations of the protective polypeptides beyond those actually tested. Thus, the data provided in the application in addition to supporting representative species also supports a combination of structure and function commensurate with the scope of the claims.

Claims 1, 8, 9, and 38 include a description of a protective polypeptide immunogen with an amino acid sequence at least 94% identical to SEQ ID NO: 3 or a fragment of said amino acid sequence comprising a sequence at least 94% identical to SEQ ID NO: 1. Claim 1 is directed to the polypeptide immunogen. Claims 8 and 9 are directed to a composition containing the immunogen and a pharmaceutically acceptable carrier, where the composition *can* provide protective immunity in a patient. Claim 38 depends from claim 8, and further describes the polypeptide

immunogen as substantially purified and the patient as a human. The present application reasonably conveys to one skilled in the art possession of the polypeptide immunogen described in claims 1, 8, 9, and 38, by providing examples of different polypeptides either shown to provide protection or, based on the present application, expected to provide protection, and providing sequence information on different *S. aureus* strains.

The present application in Example 3 provides protection data using different polypeptide immunogens containing an ORF0657nl region from SEQ ID NO: 1 against the heterologous *S. aureus* strain Becker (page 26, line 18 to page 27, line 2, Figure 3A-3C, and description of the figures on page 5, lines 16-33). The present application in Example 6 illustrates the ability of a full-length construct containing an ORF0657nl region from SEQ ID NO: 1 to provide protection against different heterologous clinical isolates (page 29, line 10 to page 29, line 21, Figures 4A-4H and the description of the figures on page 5, lines 23-32). The present application in Example 16 illustrates the use of different polypeptides to provide protection (page 50, line 30 to page 51, line 21, and Figure 10). The regions of ORF0657 used in different protective immunogens are illustrated by Figure 1 of the present application. Figure 1 illustrates the full-length COL *S. aureus* ORF0657n and the location of different regions including ORF0657nl and ORF0657nH. SEQ ID NO: 1 provides the sequence for an ORF0657nl region for *S. aureus* COL, and SEQ ID NO: 3 provides the sequence for ORF0657nH region for *S. aureus* COL. Both SEQ ID NOs: 1 and 3 have a methionine added to the amino terminus (page 8, Table 1).

The data illustrated in Examples 3, 6 and 16 identifies SEQ ID NO: 1 as sufficient to induce a protective immune response, illustrates the ability of SEQ ID NO: 1 to provide protective immunity against *S aureus* strain Becker, and illustrates the ability of longer-length polypeptides containing SEQ ID NO: 1 to provide protection against different heterologous clinical isolates of S. *aureus.* Strain Becker ORF0657n has a sequence identity of 95% to the COL ORF0657n sequence (page 29, Table 3). The different clinical isolate *S. aureus* strains have an ORF0657n differing from COL ORF0657n by up to 94% (Figures 4A-4H on page 5, lines 23-32 and Table 3 on page 28 to 29).

The ability of a particular polypeptide to induce an immune response against a heterologous strain provides important information concerning both the range of *S. aureus* that can be targeted by a particular polypeptide and variations in polypeptide structure that can be made and still retain the ability to induce protective immunity. A polypeptide inducing protective immunity generates an immune response against a target present on the challenge strain. The ability to induce an immune response against heterologous strains indicates that regions involved in the protective immune response are present in both the employed polypeptide immunogen and the challenge strain. The corresponding challenge strain sequence would be expected to also induce an immune response, for example, when used in a homologous challenge. The expectation is based on a homologous challenge involving the use of a polypeptide immunogen having the same region as the challenge strain, where in a heterologous challenge the sequence used to

induce the immune response is different from that actually present. The rejection is improperly based on the possibility that some unidentified alteration could negatively impact the ability of a protective polypeptide to continue to provide protection. The rejection fails to provide support concerning the likelihood that alterations could occur in an essential region within the described genus, such that a significant number of polypeptide immunogens within the described genus would not be protective. The rejection also fails to take into account the importance of data in the application concerning protection in heterologous strains of *S. aureus*, guidance provided concerning the OF0657nl region, and guidance concerning different ORF0657nl sequences. The Patent Office bears the initial burden of presenting a *prima facie* case of unpatentability. *In re Oetiker* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). The protection data provided in Examples 3, 6 and 16 was generated employing different constructs such as SEQ ID NO: 3, SEQ ID NO: 4 containing a carboxyl His-Tag, SEQ ID NO: 5 containing a carboxyl His-Tag, and SEQ ID NO: 28 (corresponding to a full-length sequence with a His-Tag). SEQ ID NOs: 1 and 5 provide a protective region corresponding to an ORF0657nl region (page 8, Table 1 description). SEQ ID NOs: 3 and 4 provide a protective region corresponding to an ORF0657nH region (page 8, Table 1 description).

Exhibit A, provided in the Evidence Appendix, is a sequence comparison of SEQ ID NOs: 1, 3, 4, 5 and 28. The leader sequence and the sortase cleavage site are noted in the sequence comparison. The sequence comparison also highlights amino acids at a couple of variable

amino acids present in SEQ ID NOs: 1, 3, 4, 5 and 28. Figures 2A-2E provide a sequence comparison of different ORF0657n sequences across the ORF0657nH region and include SEQ ID NOs: 1, 3, 4, and 5. The Exhibit A sequence comparison provides a useful illustration of the SEQ ID NO: 28 region expected to be involved in producing protective immunity. Both the leader sequence and LPXTG are cleavage points during cellular processing (page 19, lines 9-18). Cleavage at the LPXTG motif is indicated in Exhibit A by reference to the 'Sortase Cleavage Site'. The SEQ ID NO: 28 region expected to be present in the cell wall corresponds approximately to the ORF0657nH region of SEQ ID NO: 3. The expected SEQ ID NO: 28 cell wall region has four additional carboxyl amino acids than SEQ ID NO: 3.

Example 3 illustrates the ability of polypeptides of SEQ ID NOs: 4, 5 and 28 to provide protection against *S. aureus* strain Becker. The full-length ORF0657n *S. aureus* strain Becker contains 95% sequence identity to the full-length ORF0657n COL sequence of SEQ ID NO: 2 (page 29, Table 3). SEQ ID NOs: 1, 3, 4, 5 and 28 are based on the COL sequence (at page 8, lines 7-11 and lines 16-18). The ability of SEQ ID NO: 5 to provide protective immunity against the heterologous *S. aureus* strain Becker demonstrates the ORF0657nI region, such as that provided by SEQ ID NO: 1, is sufficient to generate a protective immune response. SEQ ID NOs: 4 and 28 are longer length polypeptides containing the SEQ ID NO: 1 0RF0657nl region. The polypeptide providing an ORF0657nl region (SEQ ID NO: 5) generated at least an equal level of protection to the polypeptide providing the ORF0657nH region (SEQ ID NO: 4). The data

provides evidence that ORF0657nH does not contain a critical region beyond that provided by the ORF0657nl region (see the present application Figure 3B and 3C). The protection data also illustrates that SEQ ID NO: 1 is representative of the scope of the claims; and that alterations to the sequences used in the application could be made, where the resulting immunogens would be protective. For example, the skilled artisan could expect the naturally occurring sequence present in the *S. aureus* Becker strain to provide protective immunity against at least strain Becker. Such an expectation is based on, for example, a polypeptide providing an ORF0657nl or ORF0657nH region based on strain Becker having a greater degree of homology to strain Becker ORF0657n than SEQ ID NOs: 4 or 5. Based on random chance, one of ordinary skill in art would expect amino acid differences between *S. aureus* strain Becker and COL to be located in different regions including the ORF0657nl. Figures 2A-2E confirm such expectation by providing evidence that differences among different ORF0657n present in different strains occur in different locations including the OFR0657nl region. A sequence comparison between the strain Becker ORF0657n, SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5 is attached as Exhibit B and provided in the Evidence Appendix. The sequence comparison confirms the evidence provided in the application, and what would be expected by one skilled in the art, concerning the presence of different alterations between COL and Becker being located in different regions.

Example 6, page 29, Figures 4A-4H, and description of the figures provided on page *5,* lines 23-31 of the present application illustrate the

ability of the polypeptide of SEQ ID NO: 28 to provide protection against different clinical strains of S. *aureus* strains. The ability of a full-length ORF0657n to provide protective immunity against different clinical isolates further supports SEQ ID NO: 1 being representative of the claimed genus; provides support for additional representative species described in the application being protective; and confirms the expectation that alterations can be made to SEQ ID NO: 1, where the resulting polypeptide retains its protective ability. The relevance of the data generated with the full-length ORF0657n for the ORF0657nI and ORF0657nH regions can be illustrated by reference to Figures 2A-2E of the present application and Exhibit A. The ORF0657nI region of SEQ ID NO: 1 illustrated in Figures 2A-2E starts at amino acid 3 and runs to the end of SEQ ID NO: 1. The ORF0657nH region of SEQ ID NO: 3 illustrated in Figures 2A-2E goes from amino acid 3 to the end of SEQ ID NO: 3. Figures 2A-2E illustrates examples of differences between SEQ ID NOs: 1 and 3, and different naturally occurring sequences. Exhibit A illustrates the processing sites of ORF0657n that produce a region expected to be present in the *S. aureus* wall. Due to processing of the leader sequence and the sortase cleavage site, a region approximately corresponding to the ORF0657nH is expected to be present. The portion of SEQ ID NO: 28 potentially involved in providing protective immunity is that portion generating an immune response against a polypeptide present on the cell wall. For SEQ ID NO: 28, the relevant region corresponds to the SEQ ID NO: 3 0RF0657nH region plus an additional four amino acids, which provides for a sequence identity of 568 amino acids out of 572 amino acids or over 99%. The

ORF0657nl region of SEQ ID NO: 1 has a significant overlap with the portion of SEQ ID NO: 28 remaining after cellular processing. The overlap contains an exact match of 445 amino acids out of 572. The overlap runs across about 78% of the relevant portion of SEQ ID NO: 28. Example 3 of the present application illustrates that the ORF0657nl region is sufficient to provide protective immunity.

Figures 4A-4H of the present application illustrate the ability of SEQ ID NO: 28 to provide protection against different heterologous clinical isolates designated CL- 10, CL- 13, CL-30, CL-18 and CL 21. With respect to the Figures 2A-2E sequence alignment: CL-10 corresponds to ID 11, CL- 13 corresponds to ID 19, CL- 18 corresponds to ID- 18, CL-21 corresponds to ID-22, and CL30 corresponds to ID24. The present application at pages 28 and 29, Table 3, recites that CL-10, CL-13, CL-30, CL-18 and CL 21 are diverse *S. aureus* strains with different degrees of sequence identity to SEQ ID NO: 2. CL-10 has 97% sequence identity to SEQ ID NO: 2, CL-13 has 99% sequence identity to SEQ ID NO: 2, CL-21 is a methicillin resistant strain with 94% sequence identity to SEQ ID NO: 2, and CL-30 has a 96% sequence identity to SEQ ID NO: 2. Based on the data with different clinical isolates, additional species described in the application that are within the genus are expected to provide protective immunity. Examples of ORF0657nl polypeptides are provided by the present application on page 13, lines 3-14. Additionally, Figures 2A-2E provide a sequence comparison illustrating differences among the different sequences. The different sequences provided in the application are relevant to support the scope of the claims. "Prophetic examples are

routinely used in chemical arts, and certainly can be sufficient to satisfy the written description requirements." *Ariad,* 598 F.3d at 1357, 94 USPQ2d at 1176. Support for *the different sequences* described in the application *being protective* is provided by the ability of SEQ ID NO: 28 to provide protection against different clinical isolates. Such protection data illustrates that ORF0657n present in different organisms can be targeted, and provides evidence that the corresponding region from other S. *aureus* strains involved in generating an immune response (e.g., ORF0657nI) could be used to provide protection.

With respect to SEQ ID NO: 1 and data provided in the application, included among the additional sequences are amino acids 1-442 of SEQ ID NO: 11; amino acids 1-442 of SEQ ID NO: 18; amino acids 1-445 of SEQ ID NO: 19; amino acids 1-454 of SEQ ID NO: 22; and amino acids 1-446 of SEQ ID NO: 24 (page 13, lines 3-13). CL-10 corresponds to SEQ ID NO: 11, CL-13 corresponds to SEQ ID NO: 19, CL-18 corresponds to SEQ ID NO: 18, CL-21 responds to SEQ ID NO: 22, and CL30 corresponds to SEQ ID NO: 24. The sequence identity provided in Table 3 for the full-length ORF0657n polypeptides and the results showing protection with different clinical isolates reasonably convey to one skilled in the art that applicants were in possession of the polypeptides described in the claims. Table 3 indicates ranges of sequence identity of different clinical isolates of up to 94% to SEQ ID NO: 2 (pages 28-29). Additional support for an at least 94% sequence identity is provided by Figures 2A to 2E, which illustrate alterations among different clinical isolates. A 94% sequence identity to SEQ ID NO: 1 provides *about 27 alterations*. In the

ORF0657nI region of SEQ ID NO: 1, CL-10 (SEQ ID NO: 11) has 10 alterations; CL-18 (SEQ ID NO: 18) has 10 alterations; CL-13 (SEQ ID NO: 19) has 7 alterations; CL-21 (SEQ ID NO: 22) has 22 alterations; and CL30 (SEQ ID NO: 24) has 11 alterations (Figures 2A-2E). The alteration to SEQ ID NO: 1 is noted by comparing highlighted regions in SEQ ID NO: 1 and other sequences, and also taking into account indicated gaps. The sequence identity for the 22 alterations is about 95% ([446-23]/446 = 95.07 %). The 446 amino acids used in the calculation are for the full-length SEQ ID NO: 1, which includes an amino terminal methionine. The sequence alignment provided in Figures 2A-2E does not show the amino acid corresponding to the SEQ ID NO: 1 amino terminus methionine for all the sequences. The presence of an amino acid other than methionine in the corresponding position would lower the sequence identity. The combined number of unique alterations for SEQ ID NOs: 11, 18, 19, 22 and 24 with respect to the ORF0657nI region of SEQ ID NO: 1 is 37 alterations. The sequence identity for the 37 alterations is about 92% ([446-37]/446).

Additional protection data using different constructs is provided by Example 16 of the application (page 50, line 30 to page 51, line 21), the results being shown in Figure 10. With respect to Figure 10, ORF0657nH (*E. coli*) corresponds to SEQ ID NO: 4 with a carboxyl His-Tag, ORF0657nI (*E. coli*) corresponds to SEQ ID NO: 5 with a carboxyl His-Tag, ORF0657nC (*E. coli*) corresponds to SEQ ID NO: 28; and ORF0657nH (yeast) corresponds to SEQ ID NO: 3 (page 7, lines 9-13). In the experiments illustrated in Figure 10, the polypeptide providing an

ORF0657nI region generated a similar level of protection to the polypeptide providing the ORF0657nH region. The data provides additional evidence that ORF0657nH does not contain a critical region beyond that provided by the ORF0657nI region. While not indicated in the application, the challenge strain employed in Example 16 was *S. aureus* strain Becker.

The rejection is improperly based on speculation concerning the potential impact of an unidentified mutation to a protective polypeptide, provides unsupported and incorrect statements concerning SEQ ID NO: 4 providing an example of a polypeptide consisting of an amino acid sequence 99.8% identical to SEQ ID NO: 1 which is not protective; provides arguments regarding a fragment described in the application that is not within the scope of claims 1, 8, 9, and 38; and refers to part of some additional data. The rejection fails to indicate why one skilled in the art would not in general expect polypeptides within at least 94% sequence identity to SEQ ID NO: 3 or containing a region with at least 94% sequence identity to SEQ ID NO: 1 to provide protection. Such an expectation is relevant, for example, in evaluating whether the polypeptides illustrated in the application are representative of the claims. The Office ignores the data concerning longer-length constructs, arguing that such constructs are not themselves within the scope of the claims. Such arguments fail to consider the data provided in the application as a whole, including the presence in the longer-length construct of a core region shown to be protective.

Appellants acknowledge that the elected species is SEQ ID NO: 1. Appellants further state the following: Claims 1 (b) and 8(b) are indicated to require the polypeptide immunogen to minimally consist of a fragment of an amino acid sequence 94% identical to SEQ ID NO: 3, wherein the fragment comprises an amino acid sequence 94% identical to SEQ ID NO: 1. The claim 7 immunogen is interpreted to require a protective immune response. The Office also indicates claim 1 as not specifying to whom the protective immune response is provided, that any amino acid may be substituted, modified, or deleted along the length of SEQ ID NO: 3 and/or SEQ ID NO: 1 as long as the polypeptide fragment retains the percent identity, with or without the further up to 20 amino acids, and that the full-length ORF0657n is not encompassed by the claims. Appellants state that they are not clear on what is meant by retaining the percent identity with or without the further up to 25 amino acids, but acknowledge that claims 1, 8, 9 and 38 refer to 'at least' 94% identity and some later claims refer to up to 25 amino acid alterations. With respect to percent identity, Appellants state that such description would allow for additional amino acids. With respect to the question raised concerning in whom the claim 1 immunogen provides protection, Appellants note that claim 1 is directed to a polypeptide immunogen and is not a method claim, and that the application illustrates the ability of polypeptide immunogens to provide protection.

The Office appears to take the position that the data provided with SEQ ID NO: 28 is not relevant to the pending claim. The argument is based on SEQ ID NO: 28 not being within the scope of the claims. It is

also indicated that SEQ ID NOs: 3, 4 and 5 are not 94% or 90% identical to SEQ ID NO: 1. The comments fail to consider data provided in the application illustrating, for example, the ability of SEQ ID NO: 1 to provide protective immunity against strain Becker and the fact that SEQ ID NO: 28 is a longer-length sequence containing an SEQ ID NO: 1 ORF0657nl region.

The Office argues that the ability of SEQ ID NOs: 4 and 5 to provide protective immunity against heterologous *S. aureus* Becker is not sufficiently representative of the claimed species and does not show a structure-function correlation sufficient to support the genus. The data generated with SEQ ID NO: 5 illustrate that the ORF0657nl region is sufficient to generate an immune response. The data using SEQ ID NOs: 4 and 5 in combination with data generated using SEQ ID NO: 28 against different clinical isolates demonstrate possession of representative species and also provide a sufficient structure function correlation.

Appellants note the Office's position and showing as to why a significant number of polypeptides within the scope of the claims would not provide protection. Appellants also note the Office's showing that a polypeptide consisting of amino acids 82-486 of SEQ ID NO: 2 is **not** protective, but is within the scope of claim 7 sequence identity-wise. Appellants note the Office's observation in Figure 3B that SEQ ID NO: 4, when having a His-Tag, appears to show statistically insignificant protection. Appellants state that the Office's comments fail to take into account the targeting of heterologous strains illustrated in the application

and fail to provide a rationale as to why a significant number of polypeptides within the claimed genus would not be protective.

Appellants further argue that to the extent *the application illustrates that amino acids 82-486 of SEQ ID NO: 2 do not provide protection*, the indicated fragment is not covered by the claims 1, 8, 9 and 38. The referenced SEQ ID NO: 2 fragment is indicated by the Office to provide a sequence identity of 91% to SEQ ID NO: 1. The 91% identity is outside the scope of the claims in the present rejection, which require the immunogen to be 94% identical to SEQ ID NO: 1. Polypeptides providing protection in heterologous protection experiments would be expected to provide protection when used in a homologous challenge. The expectation is based on a homologous challenge experiment involving an immunogen having a polypeptide region that is the same as a region present on the challenge strain, as opposed to a heterologous challenge where the immunogen has a different region than that present on the challenge strain. Given the success of the heterologous challenge experiments described in the application, the Office fails to provide a rationale or evidence as to why the skilled artisan would not expect the corresponding ORF0657nI or ORF0657nH region from other S. *aureus* strains such as CL- 11, CL- 13, CL- 18, and CL-21 to provide protection in a homologous challenge.

Appellants allege that no particular rationale or evidence is provided concerning the position on the significance of the data generated with the SEQ ID NO: 4 polypeptide. Data concerning SEQ ID NO: 4 is provided in Figures 3B and 10, which show a real and reproducible effect. Appellants state that SEQ ID NO: 4 corresponds to the ORF0657nH region and that

SEQ ID NO: 5 corresponds to the ORF0657nI region. Appellants contend that the Office appears to be taking the position that the data with the shorter ORF0657nI is sufficient to provide protection, while the longer fragment is not, and no rationale is provided for such distinction. The Office argues that Appellants were not in possession of S. *aureus* strains containing naturally occurring ORF0657nI or ORF0657nH regions; the state of the art does not document the existence of such strains; without the knowledge whether ORF0657nI or ORF0657nH is buried in the cell wall it would not be predictable whether naturally occurring ORF0657nI or ORF0657nH are protective; the employed polypeptides have not been tested for homologous protection and therefore it is not predictable that the corresponding ORF0657nI or ORF0657nH region from CL-11, CL-13, CL-18, and CL-21 would provide protection in a homologous strain; and again refers to SEQ ID NO: 2 amino acids 82-486 not being protective. The Office's arguments concerning the state of the art fail to take into account the teaching and guidance provided in the present application. The present application provides data demonstrating polypeptides corresponding to ORF657nI and ORF0657nH regions are sufficient to generate a protective immune response. Such data demonstrates that the target polypeptide is accessible to an immune response generated with polypeptides providing ORF657nI or ORF0657nH regions. The present application provides different examples of naturally occurring ORF0657nI and ORF0657nH sequences in Figures 2A-2E.

Appellants note the Office’s observation that the percent identity recited in the instant claims is relative to SEQ ID NO: 1, not to SEQ ID

NO: 2; that CL-10, CL-13, CL-30, CL-18, and CL-21 sequences do not constitute polypeptide immunogen species consisting of an amino acid sequence 94% identical to SEQ ID NO: 1 or immunogen species consisting of an amino acid sequence 90% identical to SEQ ID NO: 1; and that the corresponding regions of these sequences do not constitute polypeptides with an amino acid sequence 94% or 90% identical to SEQ ID NO: 1. The Office argues that no sequence from CL-10, CL-13, CL-30, CL-18, and CL-21 has been correlated with homologous or heterologous protection; the results with SEQ ID NO: 2 amino acids 82-486 show no protection; the results with SEQ ID NO: 4 are not significant; and refers to additional data illustrating a lack of protection for ORF0657nI in the absence of endotoxin. The 'at least 94% identity' to SEQ ID NO: 1 is supported by the expectation that polypeptides having a high degree of structural similarity to SEQ ID NO: 1 would be able to provide protection, and by data described in the application along with the sequence comparison provided in Figures 2A to 2E. The Office fails to provide any rationale or evidence as to why the skilled artisan would not expect the corresponding ORF0657nI or ORF0657nH region from other *S aureus* strains such as CL-10, CL-13, CL-30, CL-18, and CL-21 to provide protection in a homologous challenge. Indeed, the skilled artisan would expect the corresponding regions from strains such as CL-10, CL-13, CL-30, CL-18, and CL-21, when used as an immunogen in a homologous challenge, would provide protection based on providing a region with the same sequence as actually present in the challenge organism.

The Office argues for unpredictability based on the data provided with SEQ ID NO: 2 amino acids 82-486 and SEQ ID NO: 4. The referenced SEQ ID NO: 2 fragment is not covered by the claims 1, 8, 9 and 38. In arguing unpredictability based on SEQ ID NO: 4, the Office asserts that the SEQ ID NO: 4 polypeptide does not provide statistically significant protection despite an identity of 99.8% SEQ ID NO: 1. No particular rationale or evidence is provided concerning the Office's position on the significance of the data using the SEQ ID NO: 4 polypeptide. Data concerning SEQ ID NO: 4 is provided in Figures 3B and 10. Such data show a real and reproducible effect. Additionally, SEQ ID NO: 4 corresponds to the ORF0657nH region and SEQ ID NO: 5 corresponds to the ORF0657nI region. The Office appears to be taking the position that the data with the shorter ORF0657nI is sufficient to provide protection, while the longer fragment is not and no rationale is provided for such distinction. With respect to the additional data, applicants assume the Office is referring to an amendment filed August 18, 2009. The August 18, 2009 amendment provides data indicating *variability in the model* employed and that an immune response could be produced in the absence of endotoxin. The endotoxin was shown to have an effect in the BALB/C mice model. The August 18, 2009 amendment also indicates that yeast produced ORF0657nI not containing endotoxin provided protective immunity in ICR mice.

The Office indicates that no requirement was made that the claimed polypeptides provide protection against each and every *S. aureus* in a non-human or human host and that von Eiff *et al.* (*Diagn. Microbiol. Infect.*

Dis. 58:297-302, 2007) was properly cited by the Patent Office to document the existence of immunologically heterogeneous or distinct types among *S. aureus.* It was Applicants' understanding that the von Eiff *et al.* reference was previously cited on page 9 of the Office Action dated November 24, 2009 to support an argument that the present polypeptides need to provide protection against homologous or heterologous strain, serotype, *Spa* type, phage type or capsular type of *S. aureus.*

Appellants acknowledge the Office's documentation that the structure or the amino acid sequence of the Becker strain of *S. aureus* was **not** disclosed in the instant application at the time of filing. Appellants acknowledge the telephonic conversation that took place between Appellants' representative Mr. Sheldon Heber and the Examiner of record, wherein attorney Sheldon Heber indicated that the Becker ORF0657n sequence is **not** a part of the instant application, and that the Becker sequence was not provided in the application. Appellants state that *S. aureus* strain Becker is *a laboratory strain* of S. *aureus*; the ORF0657n strain Becker sequence has a sequence identity of 95% to SEQ ID NO: 2; and the application reasonably conveys to the skilled artisan that applicants had possession of the strain Becker ORF0657 sequence.

The Office argues the issue of host species in which protection is to be provided is very relevant in light of Applicants' data. According to the Office, based on data submitted in Amendment/Remarks filed June August 18, 2008, ORF0657nl would not be expected to provide protection in a human patient including an immunodeficient, immunosuppressed and immunocompromised patient on its own. Reference to immunodeficient,

immunosuppressed and immunocompromised patients appears to be an argument that applicants must show possession of a polypeptide that provides protective immunity in a patient lacking the ability to induce an immune response. Given the teaching in the application concerning use of the polypeptides to provide protective immunity, the skilled artisan could readily employ the polypeptide in a host having a functioning immune system to respond to the immunogen. Given the examples provided in the application using animal models, additional effectiveness in a non-human or human (e.g., immunodeficient, immunosuppressed and immunocompromised patient) does not need to be shown. Appellants assume that the rejection is based on enablement for certain uses and assert that the enablement requirement is met if the description enables any mode of making and using the claimed invention.

The Office notes that alterations to SEQ ID NO: 1 encompass alterations, substitutions and deletions within SEQ ID NO: 1, argues that the Office has previously established the polypeptides having any degree of structural similarity are not necessarily expected to have similar properties absent a concrete structure-function correlation, and cites Colman P.M. (*Research Immunol.* 145:33-36, 1994), McGuiness *et al.* (*Mol. Microbiol.* 7:505-514, Feb 1993), and McGuiness *et al.* (*Lancet* 337:514-517, March 1991) for the argument that a change of a single amino acid can disrupt antibody-polypeptide binding. The references concerning antibody-peptide interactions are silent as to the likelihood that a particular alteration would prevent a longer-length polypeptide, shown to be protective, from maintaining its ability to provide protection. The

possibility that some unknown alteration in an amino acid residue may impact a particular protein-antibody interaction, does not equate to a significant number of polypeptides within the scope of the claims losing its ability to provide protective immunity. The rejection takes the position that if a single unidentified alteration within the 446 amino acids of SEQ ID NO: 1 may render the polypeptide not protective, then written description is lacking. Such an argument fails to consider what is reasonably conveyed to the skilled artisan by the percent of polypeptides within the described genus that are active. SEQ ID NO: 1 is 446 amino acids in length and may contain more than one epitope providing a beneficial effect. Epitopes providing beneficial effects could include one or more B-cell epitopes and one or more T-cell epitopes. The T-cell epitopes would drive a cell mediated response involving the presentation of short antigens on antigen presenting cells. Appellants state that claim 4 further describes the polypeptide immunogen of claim 1 by indicating that the immunogen consists of an amino acid sequence at least 94% identical to SEQ ID NO: 1, SEQ ID NO: 3 or SEQ ID NO: 42. SEQ ID NO: 3 provides an ORF0657nH region and SEQ ID NO: 42 provides an ORF0657nI+ region. (Figure 1 of the application.) The Patent Office rejection does not provide any additional basis for rejecting claim 4 as opposed to claim 1. The rejection appears to be based on reference to at least 94% identical to SEQ ID NO: 1. The application provides sufficient written description support for at least 94% identical to SEQ ID NO: 1. To the extent the rejection to claim 4 is based on reference in the claim to 94% identical to

SEQ ID N: 42, different ORF0657nI+ sequences are referenced in the application on page 13, line 28 to page 14, line 5.

Appellants submit that the data and guidance in the application provide written description support for claims 33, 39, 40, and 49 which further describe the polypeptide immunogen by indicating that the immunogen has up to 25 amino acid alterations from SEQ ID NO: 1. The data and guidance in the application provide written description support for claims 34, 41, 42, and 50 which further describe the polypeptide immunogen by providing for 10 amino acid alterations from SEQ ID NO: 1. The data and guidance in the application provide written description support for claims 35, 43, 44 and 51 which further describe the polypeptide immunogen by indicating that the immunogen has up to 5 amino acid alterations from SEQ ID NO: 1. The rejection does not specially present arguments concerning 25, 10 or 5 amino acid alterations, but rather takes the position that any number of alterations from SEQ ID NO: 1 lacks written description. The application provides sufficient written description support for at least 94% identical to SEQ ID NO: 1, which would encompass up to 25, 10 or 5 amino acid alterations. The description of 25, 10 or 5 alterations provides for a stronger structural relationship to polypeptides shown to be protective than the at least 94% identity. The stronger structural relationship to polypeptides such as SEQ ID NO: 1 and corresponding ORF0657nI regions illustrated in the application, provides additional support for the polypeptides being representative of the genus. The Office fails to provide evidence as to why the skilled artisan would expect a significant number of polypeptides having up to 25, 10 or 5

alterations from SEQ ID NO: 1 not to be protective. The present application provides evidence using heterologous protection studies that alterations could be made where the resulting polypeptide is protective. Additional support for up to 10 alterations is provided in the application by Figures 2A to 2E which illustrate different examples of amino acid alterations occurring throughout the ORF0657nI and ORF0657nH regions. For example, in the ORF0657nI region, CL-10 (SEQ ID NO: 11) has 10 alterations; CL-18 (SEQ ID NO: 18) has 10 alterations; CL-13 (SEQ ID NO: 19) has 7 alterations; CL-21 (SEQ ID No: 22) has 22 alterations; and CL30 (SEQ ID NO: 24) has 11 alterations. The combined number of unique alterations for SEQ ID NOs: 11, 18, 19, 22 and 24 with respect to the ORF0657nI region of SEQ ID NO: 1 is 37 alterations. The consideration of additional strains further increases the number of illustrated alterations.

Appellants contend that the application provides written description support for claim 7, which is directed to an immunogen consisting of an amino acid sequence at least 90% identical to SEQ ID NO: 1 and one or more additional regions or moieties covalently joined to the sequence at the carboxyl terminus or the amino terminus. Support for the at least 90% identity is provided in Figures 2A-2E. The ORF0657nI region in Figures 2A-2E goes from amino acid 3 to amino acid 455 and illustrates examples of differences between SEQ ID NO: 1 and different naturally occurring sequences. Adding the total differences between SEQ ID NO: 1 and the other strains provides for 49 unique differences. Dividing 49 by the overall size of SEQ ID NO: 1 (446 amino acids) illustrates a sequence identity of 89%, which provides for a greater variation that the ‘at least 90%’

sequence identity. The 446 amino acids used in the calculation are for the full-length SEQ ID NO: 1, which includes an amino terminal methionine. The sequence alignment provided in Figures 2A-2E does not show the amino acid corresponding to the SEQ ID NO: 1 amino terminus methionine for all the sequences. The presence of an amino acid other than methionine in the corresponding position would lower the sequence identity. The heterologous protection data provided in the application illustrates that alterations could be made to SEQ ID NO: 1 and the resulting polypeptide would be protective. With respect to claim 7, the Office argues that SEQ ID NO: 2 amino acids 82-486 has a sequence identity of 91% to SEQ ID NO: 2 and does not provide protection. To the extent that fragment is not protective, such a fragment is at the outer limit of claim 7 and is functionally excluded by the claim.

The Office's Rebuttal to Appellants' arguments:

Appellants are correct in noting that written description of a genus requires a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus. *University of California v. Eli Lilly & Co.,* 119 F.3d 1559, 1568-1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The present application however does not reasonably convey to those skilled in the art that the inventors had possession of the claimed broad genus as of the filing date by providing representative species of polypeptides or immunogens within the claimed vast genus.

The present application does not reasonably convey to those skilled in the art that the inventors had possession of the full scope of the claimed invention as of the filing date of the instant application. Contrary to Appellants' assertion, the Office has provided sufficient basis, rationale, and evidence from Appellants' own specification as well as Appellants' own additional data in establishing the lack of possession of a representative number species encompassed within the claimed broad genus. As set forth previously and as described in detail in the following sections, the Office has clearly met the burden of presenting a *prima facie* case of lack of sufficient structure-function correlation combined with lack of predictability. The Office has concretely established why one skilled in the art would not expect a representative number of polypeptide immunogen species falling within the genus to provide protection against *S. aureus*.

The Appellants' reference to the additional data from their amendment filed August 18, 2009 is not understood. No amendment was filed by Appellants in the instant application in August of 2009.

With regard to Appellants' remarks on the Office's citation of von Eiff *et al.* (*Diagn. Microbiol. Infect. Dis.* 58:297-302, 2007, of record), contrary to Appellants' assertion, page 9 of the Office Action dated November 24, 2009 does not even mention about the reference of von Eiff *et al.* While analyzing the scope of the instant claims, the reference of von Eiff *et al.* was cited in the original rejection to document that clinical isolates of pathogenic *S. aureus* represent a huge genus belonging to immunologically very diverse isolates. That the limitation '*S. aureus*' in the claims is not limited to a laboratory strain of S. *aureus* such as Becker, but

represents a vast genus of geographically, pathologically, taxonomically, and genetically diverse serotypes, *Spa* types, phage types, and capsular types of pathogenic *S. aureus,* is very well known in the art.

As set forth previously, the elected polypeptide species examined in the instant application is SEQ ID NO: 1. All independent claims use the closed claim language 'consisting of' with regard to the amino acid sequence of the claimed product. The purified polypeptide immunogen claimed in claim 1(b) and recited in claim 8(b) is minimally required to (A) *consist* of a *fragment* of an amino acid sequence 94% identical to SEQ ID NO: 3, wherein the *fragment* comprises an amino acid sequence 94% identical to SEQ ID NO: 1 (i.e., 6% non-identical); and (B) provide protective immune response against *S. aureus.* The limitations in claims 1(b) and 8(b): 'polypeptide immunogen *consisting of* … a fragment of said amino acid sequence …. wherein said … *comprises*', is interpreted as permitting the recited percent sequence identity or amino acid alterations *within* the claimed polypeptide immunogen fragment. The generic limitation 'protective immune response against *S. aureus*' in claim 1 does not specify to whom the protective immune response is provided and therefore encompasses protection provided to any host species. The polypeptide immunogen of the dependent claim 4 is required to consist of an amino acid sequence at least 94% identical to SEQ ID NO: 1 and is required to provide protective immunity against *S. aureus*. The polypeptide immunogens claimed in the dependent claims 33-35 and 39, 31 and 43 encompass those that differ from SEQ ID NO: 1 by up to 25, 10, or 5 amino acid alterations, and are still required to provide protective

immunity against *S. aureus*. The dependent claims 38, 40, 42 and 44 are required to be substantially purified and are required to provide protective immunity against *S. aureus* in a human patient. Thus, contrary to Appellants' assertion, claims 33, 39, 40, and 49 are not drawn to polypeptides having 'stronger structural relationship to polypeptides shown to be protective', but to protective polypeptide variants containing up to 25 unspecified and undefined alterations within SEQ ID NO: 1. The limitation 'patient is a human' in claims 38, 40, 42 and 44 does not exclude, but includes immune-sufficient, immune-deficient, immunocompromised, and immunosuppressed human patients, including cancer patients, AIDS patients, patients with organ transplantation, and patients with end-stage kidney disease etc., among whom multiple drug-resistant and vancomycin-resistant *S. aureus* infections are known to cause increased mortality and morbidity. The limitation 'patient is a human' also includes neonates, infants, pediatric and geriatric patients as well.

The immunogen claimed in the independent claim 7 is minimally required to (A) consist of an amino acid sequence 90% identical to SEQ ID NO: 1 (i.e., 10% non-identical) and one or more additional regions covalently joined thereto either at the carboxyl or the amino terminus as recited therein, facilitating the stability of an unspecified polypeptide; and (B) provide protective immune response against *S. aureus.* Although claim 7 does not include the recitation of providing 'protective immune response against *S. aureus*', the limitation 'immunogen' as defined at line 25 of page 2 of Appellants' specification is required to have the ability to provide protective immunity, consistent with the intended prophylactic (i.e.,

vaccine) applications. Specifically, at line 25 of page 2 of the specification, Appellants expressly state that the following:

> Reference to "immunogen" indicates the ability to provide protective immunity.

Claims are interpreted in light of the specification. USPTO personnel are to give claims their broadest reasonable interpretation *in light of the supporting disclosure*. Where an explicit definition is provided by the applicant for a term, that definition will control interpretation of the term as it is used in the claim. *Toro Co. v. White Consolidated Industries Inc.*, 199 F.3d 1295, 1301, 53 USPQ2d 1065, 1069 (Fed. Cir. 1999) (meaning of words used in a claim is not construed in a "lexicographic vacuum, but in the context of the specification and drawings."). With particular regard to the claim language used in the instant claim 7, the paragraph bridging pages 2 and 3 of Appellants' specification states the following [Emphasis added]:

> Another aspect of the present invention describes **an immunogen comprising an amino acid sequence that provides protective immunity against *S. aureus*.** The immunogen comprises an amino acid sequence at least 90% identical to SEQ ID NO: 1 and one or more additional regions or moieties covalently joined at the carboxyl terminus or amino terminus, wherein each region or moiety is independently selected from a region or moiety having at least one of the following properties: enhances the immune response, facilitates purification, or facilitates polypeptide stability.

Therefore, the immunogen claimed in the independent claim 7 is *required* by definition to provide protective immunity against *S. aureus*. The at least 90% identical immunogen claimed in the dependent claims 49-51 encompass those that differ from SEQ ID NO: 1 by up to 25, 20 or 5 amino acid alterations, and are still required to provide protective immunity against *S. aureus* as required by Appellants' express definition of the limitation 'immunogen'. See *supra*. Appellants' current argument that the

immunogen of claim 7 is not associated with the protective function is contrary to the express definition provided in the as-filed specification.

Contrary to Appellants' arguments, the scope of the instantly claimed genus is not limited to a single polypeptide or immunogen species consisting of an amino acid sequence 100% identical to SEQ ID NO: 1 with no amino acid alterations therein, or to a 99.8% identical variant species containing a single amino acid alteration exclusively after the N-terminal methionine of SEQ ID NO: 1. Instead, the claimed broad genus collectively encompasses a huge number of polypeptide variant species or immunogen variant species *consisting of* an amino acid sequence that is:

(1) 90% identical to SEQ ID NO: 1;
(2) 91% identical to SEQ ID NO: 1;
(3) 92% identical to SEQ ID NO: 1;
(4) 93% identical to SEQ ID NO: 1;
(5) 94% identical to SEQ ID NO: 1;
(6) 95% identical to SEQ ID NO: 1;
(7) 96% identical to SEQ ID NO: 1;
(8) 97% identical to SEQ ID NO: 1;
(9) 98% identical to SEQ ID NO: 1; and
(10) 99.0% identical to SEQ ID NO: 1,

and differing from SEQ ID NO: 1 by up to 5, 10 and 25 amino acid alterations, wherein the encompassed polypeptide variant species as recited and the immunogen variant species as required by definition, are required to provide protective immunity against homologous or heterologous *S. aureus* in a human or non-human patient or subject.

Thus, the instant claims encompass a vast genus of polypeptide immunogen variants that are fragment variants of SEQ ID NO: 3 and are further variants of SEQ ID NO: 1, having up to 6% non-identity to SEQ ID NO: 3 and SEQ ID NO: 1 (claims 1 and 8), and a vast genus of immunogen variants with up to 10% non-identity to SEQ ID NO: 1 (claim 7), and differing from SEQ ID NO: 1 by up to 5, 10 or 25 amino acid alterations, each having the requisite ability to provide protective immunity against *S. aureus*. Any amino acids along the length of SEQ ID NO: 3 and/or SEQ ID NO: 1 including the non-amino terminal regions, may be substituted, modified, or deleted as long as the polypeptide fragment retains the percent identity or amino acid alterations as recited.

It is important to note that the percent identity recited in the instant claims covering the elected species is relative to SEQ ID NO: 1, and is not relative to SEQ ID NO: 2 and is not relative to SEQ ID NO: 28.

The amino acid sequence of SEQ ID NO: 2, comprising therein the SEQ ID NO: 1 without its amino terminal methionine, is the *full-length* COL ORF0657n polypeptide. The full-length polypeptide was known in the art at the time of the invention as taught by Foster *et al*. (US 6,841,154). See the art rejection made at paragraph 14 of the Office Action mailed 12/15/08. Appellants have expressly acknowledged previously that the full-length ORF0657n sequence is *excluded* from the claimed invention. For example, at third full paragraph on page 9 of the amendment/remarks filed 08/18/08, Appellants stated the following [Emphasis added]:

> 'Claim 1 **excludes** SEQ ID NO: 2'.

Again, at first full paragraph on page 20 of Appellants' amendment/remarks filed 03/13/09, Appellants stated the following [Emphasis added]:

> Claims 1, 5, 7, and 8 were amended as discussed above, so that **the full-length ORF0657n sequence is <u>not</u> covered**. Claims 3, 4, 6, 7, 33-35, and 37-44 as previously presented provided for less than the full-length sequence.

Thus, by Appellant's own admission, SEQ ID NO: 2 is not covered by the independent claims 1, 7 and 8.

With regard to claim 7, it must be noted that since the immnuogen claimed in claim 7 is not required to be purified, it encompasses non-isolated and non-purified immunogens and reads on *S. aureus* strains *consisting of* SEQ ID NO: 1 or its 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% and 99% identical variants. However, Applicants were not in possession of *S. aureus* strains containing naturally occurring ORF0657nl or ORF0657nH region. The state of the art at the time of the invention does not document the existence of such *S. aureus* strains in nature. Furthermore, without the knowledge or specific disclosure on whether or not the ORF0657nl or ORF0657nH region is buried in the cell wall or surface-exposed partially or fully, a skilled artisan would not expect *S. aureus* strains containing the allegedly naturally occurring ORF0657nl or ORF0657nH region to be protective.

With regard to Applicants' argument of SEQ ID NO: 28 being representative of the claimed broad genus of at least 90% or at least 94% identical polypeptide immunogen variants, the following must be noted. First, the percent identity recited in the instant claims is relative to SEQ ID NO: 1, not relative to SEQ ID NO: 28. The rejection of record is pertinent

to polypeptide immunogen variants having up to 6% and 10% variations, substitutions, or modifications within an amino acid sequence *consisting of* SEQ ID NO: 1, with or without additional moieties either at the amino terminus or at the carboxyl terminus. The SEQ ID NO: 28 on the other hand is the His-tagged *full-length* SEQ ID NO: 2 containing an amino acid sequence that is 99.8% identical to SEQ ID NO: 1 plus additional amino acids, not only at the amino terminus, but also at the carboxyl terminus of SEQ ID NO: 1. See Figures 1B and 1C and Appellants' evidence Exhibit 1 or Appendix A. Accordingly, since SEQ ID NO: 2 itself is excluded from the scope of the instant claims (see Appellants' statement *supra*), SEQ ID NO: 28 of the instant specification, which is longer than SEQ ID NO: 2, is also excluded from the scope of claims 1 and 8 as well as claim 7. Furthermore, as Appellants have acknowledged previously, the ORF0657nI region of SEQ ID NO: 1 that overlaps with a portion of SEQ ID NO: 28 is 78% of SEQ ID NO: 28. See second paragraph on page 11 of Appellants' amendment/remarks filed 02/24/2010. Additionally, SEQ ID NO: 28, SEQ ID NO: 2, and the sequences depicted in Figures 2A-2E other than SEQ ID NO: 1 and 5, are *not* a fragment of a polypeptide immunogen consisting of SEQ ID NO: 3 or a fragment of a polypeptide immunogen consisting of an at least 94% identical variant of SEQ ID NO: 3. SEQ ID NO: 28 comprises a polypeptide that is 99.8% identical to SEQ ID NO: 1 with a single amino acid addition at the amino terminus of SEQ ID NO: 1 after methionine, but does not fall within the scope of the instant claims because it contains additional amino acids both at the amino and carboxyl termini of SEQ ID NO: 1. SEQ ID NO: 28 does not comprise, let

alone consist of, an amino acid sequence variant that is 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99.0% identical to SEQ ID NO: 1, or such an amino acid sequence variant differing from SEQ ID NO: 1 by up to 5, 10 or 25 amino acid alterations. Furthermore, the ORF0657nI-equivalent region of SEQ ID NO: 2 or SEQ ID NO: 28 does not constitute a 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99.0% identical variant species of an amino acid sequence consisting of SEQ ID NO: 1, when sequence identity is determined using an art-recognized algorithm. Therefore, SEQ ID NO: 28 and SEQ ID NO: 2 do not fall within the scope of the instant claims.

With regard to Appellants' statement that SEQ ID NOs: 3, 4 and 5 are the tested sequences that are covered by instant claims 1 and 8 and that these sequences are representative of the claimed broad genus, the following must be noted. The SEQ ID NO: 3 as well as SEQ ID NO: 4 and SEQ ID NO: 5 polypeptide immunogen species are **not** 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99.0% identical variants of an amino acid sequence *consisting of* SEQ ID NO: 1 differing from SEQ ID NO: 1 by 2-5, 10 or 25 amino acids. With regard to claims 1(b), 8(b) and 7, purified SEQ ID NO: 4 is representative of one single species of a purified immunogen consisting of an amino acid sequence 99.8%% identical to SEQ ID NO: 1 with a single amino acid addition after the N-terminal methionine and having well over 20 additional moities at the amino terminus of SEQ ID NO: 1. SEQ ID NO: 5 is a purified polypeptide immunogen species consisting of an amino acid sequence 99.8% identical to SEQ ID NO: 1, with no additional amino acid moieties at the carboxy

terminus of SEQ ID NO: 1. SEQ ID NO: 3 is representative of one single species of a purified immunogen consisting of an amino acid sequence 100% identical to SEQ ID NO: 1 and having well over 20 additional amino acid moities at the carboxy terminus of SEQ ID NO: 1. With regard to claims 1(b) and 8(b), SEQ ID NO: 4 is longer than SEQ ID NO: 3 (see Table 1 and Appellants' evidence Exhibits A and B) and therefore, does not meet the limitation 'purified polypeptide immunogen *consisting of* a *fragment* of an amino acid sequence at least 94% identical to SEQ ID NO: 3'. The SEQ ID NOs: 3-5 are encompassed within the scope of claim 7.

Contrary to Appellants' assertion, the ability of SEQ ID NOs: 4 and 5 to provide moderate protection of about 42% in immune-sufficient mice immunized therewith against *S. aureus* laboratory strain Becker when administered with an adjuvant (see Figure 10), compared to the 20% protection seen in control mice immunized with the AHP adjuvant alone, demonstrates that it is critical for the claimed sequence species to have at least 99.8% sequence identity to SEQ ID NO: 1 and **not** to have any amino acid alterations along the length of SEQ ID NO: 1 except a single N-terminal amino acid addition after its first methionine, in order to remain moderately protective against a laboratory strain of *S. aureus* in an immune-sufficient animal model. The ability of SEQ ID NO: 3 to provide similar moderate protective immunity against *S. aureus* strain Becker when administered with an adjuvant (see Figure 10) demonstrates that a purified immunogen consisting of an amino acid sequence 100% identical to SEQ ID NO: 1 and having additional more than 20 amino acid moieties at the carboxyl terminus of SEQ ID NO: 1, is protective against a

laboratory strain of *S. aureus* in an immune-sufficient animal model. However, these three species are **not** sufficiently representative of the claimed vast genus that encompasses therein polypeptide immunogen fragment variants having 94%, 95%, 96%, 97%, 98% or 99.0% identity to SEQ ID NO: 3, wherein said fragment variants comprise an amino acid sequence having 94%, 95%, 96%, 97%, 98% or 99.0% identity to SEQ ID NO: 1 and differing from SEQ ID NO: 1 by up to 5, 10, or 25 amino acid alterations, including such alterations in non-N-terminal regions of SEQ ID NO: 1. These three species are also not sufficiently representative of the claimed broad genus encompassing immunogen species having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99.0% sequence identity to an amino acid sequence *consisting of* SEQ ID NO: 1 and differing from SEQ ID NO: 1 by up to 5, 10, or 25 amino acid alterations including such alterations in non-N-terminal regions of SEQ ID NO: 1. Furthermore, it is important to note that SEQ ID NO: 4, even when administered with the AHP adjuvant, did not provide protection against *S. aureus* in an immune-sufficient mouse model that was statistically significant compared to the protection conferred by the AHP adjuvant alone in control mice. This consistent and non-reproducible protection is discussed in the subsequent section of this Examiners' Answer that highlights the issue of protective unpredictability.

With regard to Appellants' argument on the longer-length polypeptide SEQ ID NO: 28 being representative of the claimed broad genus and its alleged ability to provide heterologous protection, the protection experiment results from Figure 4 must be noted. The experiments

showing the alleged heterologous protection were all performed by administering SEQ ID NO: 28, which is a His-tagged SEQ ID NO: 2 and is not an immunogen *consisting of* an amino acid sequence 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 1 and differing from SEQ ID NO: 1 by up to 5, 10, or 25 alterations, and/or containing one or more additional regions or moities covalently linked to said sequence at either the carboxyl *or* the amino terminus. The SEQ ID NO: 28 polypeptide, upon administration to mice in an immune-sufficient mouse model of *S. aureus* infection, induced approximately 80% death (not 80% survival) of the animals immunized therewith, following challenge infection with one of the three different clinical isolates of *S. aureus,* CL-10, CL-13, and CL-18. See Figure 4A, 4D and 4G. The SEQ ID NO: 28 polypeptide showed a death rate almost equal to the one induced in control mice immunized with the AHP adjuvant alone. See Figure 4A. Accordingly, a longer than full-length polypeptide causing about 80% death of the immunized mice or showing a death rate almost equal to the one induced in control mice immunized with an adjuvant alone, is not viewed by those of skill in the art as a polypeptide immunogen conferring *protection* to heterologous isolates of *S. aureus* and as a polypeptide immunogen representative of the claimed broad genus of protective polypeptide or immunogen variants.

Contrary to Appellants' assertion, whether or not SEQ ID NO: 1 is sufficient to generate a protective immune response against *S. aureus* is not the issue. Instead, that SEQ ID NO: 1 is not sufficiently representative of the claimed broad genus which encompasses 90%, 91%, 92%, 93%,

94%, 95%, 96%, 97%, 98%, or 99.0% identical polypeptide immunogen species capable of providing protective immunity against *S. aureus,* is the issue. Contrary to Appellants' argument, a protective polypeptide immunogen consisting of an amino acid sequence that is 100% identical to SEQ ID NO: 1 alone is not and cannot be representative of the full scope of the instant claims, but is representative only of one protective polypeptide immunogen species within the claimed broad genus that consists of an amino acid sequence with no amino acid alterations within SEQ ID NO: 1.

A part of Figure 1A illustrates the location of SEQ ID NO: 1 without its amino terminus methionine within the full-length amino acid sequence of SEQ ID MNO: 2 from COL strain of *S. aureus*. See first and third filled rectangles in Figure 1A. The brief description of the drawing for Figure 1A on page 5 of Appellants' specification states that the ORF0657nI species, SEQ ID NO: 1, was protective. See third filled rectangle from the top. The percent survival of mice associated with this protection induced by SEQ NO: 1 and the strain of *S. aureus* used in the challenge, have not been disclosed. Whether or not this protection was conferred against homologous or heterologous strain of *S. aureus* is not disclosed. The Office has assumed that this SEQ ID NO: 1-induced protection is at least a moderate protection similar to the one depicted in Figure 10 for SEQ ID NO: 5, and is not similar to the alleged protection represented by about 80% death of immunized mice as illustrated via Appellants' Figures 4A, 4D and 4G for SEQ ID NO: 28, and is not the statistically insignificant protection as illustrated via Appellants' Figure 3B for SEQ ID NO: 4.

Accordingly, it was determined that Appellants have shown possession of, or established structure-function correlation for claims drawn to a purified polypeptide consisting of an amino acid sequence of SEQ ID NO: 1, or consisting of SEQ ID NO: 1 and up to 20 additional amino acids either at its carboxyl terminus or at its amino terminus. The subject matter of such claims has been previously indicated to be allowable. See paragraph 19 of the Advisory Action mailed 03/25/10. Therefore, Appellants are incorrect in alleging that the Office fails to consider data provided in the application illustrating the ability of SEQ ID NO: 1 to provide protection.

With regard to the Appellants' assertion that an immunogen with 91% sequence identity to SEQ ID NO: 1 is at the outer limit of claim 7, the following must be noted. Claim 7 is drawn to an immunogen consisting of an amino acid sequence that is at least 90% identical to SEQ ID NO: 1, and is one of the claims included in the rejection of record. Given Appellants' own definition of the term 'immunogen' expressly stated at line 25 of page 2 of their specification, a 91% identical immunogen variant is, both structurally and functionally, still well within the scope of at least 90% immunogen variants of the instant claim 7. The only polypeptide species *consisting of* an amino acid sequence that is 91% identical to SEQ ID NO: 1 that was in Appellants' possession *at the time of the invention* was the polypeptide identified as fragment 2 in Figure 1A. In Figure 1A, the amino acid residues 42-486 of SEQ ID NO: 2 constitute the full-length SEQ ID NO 1 without the amino-terminal methionine. The fragment 2 consists of amino acids 82-486 of SEQ ID NO: 2 and qualifies as a polypeptide with 91% sequence identity to SEQ ID NO: 1, and therefore, sequence identity-

wise, certainly falls well within the scope of the immunogen consisting of an amino acid sequence *at least 90%* identical to SEQ ID NO: 1 as claimed in claim 7. However, the structure of this 91% identical fragment 2 has been definitively correlated by Appellants with lack of protection against a strain of *S. aureus*. See third full paragraph of page 8; fragment 2 in Figure 1A; and the Brief Description of the Drawing for Figure 1A on page 5 of Appellants' specification. Clearly, Appellants were not in possession of even one single 90% identical immunogen species that provided protective immunity against any strain of *S. aureus* in an animal, let alone a human or human patient. The percent identity calculated by Appellants by adding what appear to be the total differences between SEQ ID NO: 1 and the full-length sequences from *all other strains* to get a magic number of 49 unique differences and dividing 49 by the overall size of SEQ ID NO: 1 (446 amino acids) to come up with a sequence identity of 89%, is not an art-recognized way of calculating percent sequence identity. This method fails to align each of the individual ORF0657nI sequence from Figures 2A-2E with SEQ ID NO: 1 in order to identify the number of differences in each sequence and compare it the SEQ ID NO: 1 to obtain the percent identity using an art-accepted algorithm.

With regard to Appellants' remarks on the amino acid sequences disclosed in Figures 2A-2E being representative of the claimed vast genus, the following must be noted. First, the percent identity recited in the instant claims is relative to SEQ ID NO: 1, not relative to full length sequences. The CL-10, CL-13, CL-30, CL-18 and CL 21 sequences depicted in Figures 2A-2E do not constitute SEQ ID NO: 1-corresponding

polypeptide immunogen species *consisting of* an amino acid sequence 94% identical to SEQ ID NO: 1, or immunogen species consisting of an amino acid sequence 90% identical to SEQ ID NO: 1. The CL-10, CL-13, CL-30, CL-18 and CL-21 sequences are full-length sequences similar to the COL full-length sequence, SEQ ID NO: 2, which has been expressly stated by Appellants as being *excluded* from the scope of the claims. The reference made in the advisory action to additional amino acids is pertinent to the additional regions or moieties required to be present at the carboxyl or the amino terminus of the immunogen claimed in claim 7. With regard to Appellants' remark that 94% sequence identity to SEQ ID NO: 1 provides about 27 alterations, it must be noted that not one single individual sequence from Figures 2A-2E contains even 24 or 25 alterations in the ORF0657nI region, let alone 27 alterations and the requisite protective function. Contrary to Appellants' assertion, SEQ ID NO: 11 (CL-10); SEQ ID NO: 18 (CL-18); SEQ ID NO: 19 (CL-13); SEQ ID NO: 22 (CL-21); and SEQ ID NO: 24 (CL-30) having up to 22 alterations in the non-N-terminal ORF0657nI regions do not and cannot provide evidence of possession at the time of filing, since the ORF0657nI regions of these full-length sequences have not been correlated with the requisite function, i.e., homologous or heterologous protection, with or without an adjuvant, in an immune-sufficient animal subject, let alone a human or non-human patient, including an immune-deficient or an immunocompromised human or non-human patient. Not a single amino acid sequence from Figures 2A-2E containing numerous amino acid alterations along the non-amino terminal parts of the ORF0657nI-

equivalent region has been correlated with protection. Not one single amino acid sequence from Table 3 is 90% identical to SEQ ID NO: 1 and has been correlated with protection against homologous or heterologous *S. aureus.* In sum, the protection conferred by an amino acid sequence consisting of SEQ ID NO:1 or an amino acid sequence differing from SEQ ID NO: 1 by a single amino acid addition after the N-terminal methionine cannot be extrapolated to SEQ ID NO: 11 (CL-10); SEQ ID NO: 18 (CL-18); SEQ ID NO: 19 (CL-13); SEQ ID NO: 22 (CL-21); and SEQ ID NO: 24 (CL-30), because these sequence comprise multiple amino acid alterations along the non-amino terminal parts of the ORF0657nI-equivalent region.

Contrary to Appellants' assertion, the naturally occurring sequence present in the *S. aureus* Becker strain is **not** covered by the instant claims. The *as-filed* specification provides no structure and no structure-protective function correlation for a polypeptide or immunogen consisting of the Becker ORF0657n sequence. At the time of the invention, Applicants were not in possession of a polypeptide or immunogen consisting of the Becker ORF0657n sequence that provided protective immunity against any strain of *S. aureus* in an animal or a human patient. The Becker ORF0657n sequence, let alone its ORF0657nI sequence, was **not** a part of the as-filed instant application and the instant sequence listing. The instant specification at the time of filing provided no disclosure on the protective immunity, if any, conferred by the Becker ORF0657n sequence or its ORF0657nI sequence, against homologous or heterologous *S. aureus.* Attorney Heber confirmed that the Becker

ORF0657n sequence is not a part of the instant application in a telephone communication on 03/08/2010. The 95% identity indicated in Table 3 on page 29 of the instant specification for the Becker full-length polypeptide sequence is relative to the full-length SEQ ID NO: 2 (see lines 5 and 6 on page 29 of the instant specification), and not relative to SEQ ID NO: 1. Additionally, there is no evidence in the as-filed specification that native or altered COL sequence variants falling within the full scope of the claimed genus were tested for protection against the homologous COL strain of *S. aureus.*

With regard to Appellants' statement on the described genus being 'active', it must be noted that the instant claims do not require the recited polypeptide variants or immunogen variants to be merely 'active', but require said variants to be protective against a *S. aureus*, i.e., homologous *S. aureus*, and/or any strain, serotype, capsular type, Spa type, *or* phage type of *S. aureus* in a human or non-human patient or subject. The epitopes present within the claimed genus of polypeptide immunogen variants are required to have protective effects, not some unspecified 'beneficial effects'. Not one single B-cell or T-cell epitope that is responsible for homologous or heterologous protection against *S. aureus* in a human or non-human patient or subject has been identified in the as-filed specification such that one of skill in the art could avoid modifying the regions around those epitopes while retaining requisite protective function of the encompassed species. Instead, the results from Figure 1A of the as-filed specification concretely demonstrate the total lack of one or more B-cell and/or T-cell protective epitopes in the fragments spanning amino

acid positions 42-196 and amino acid positions 82-486 within SEQ ID NO: 2, i.e., *the regions spanning the entire length of SEQ ID NO: 1*. This would indicate to those of skill in the art of the potential discontiguous or conformational nature of the protective epitope(s) within SEQ ID NO: 1, requiring one or more amino acid residues from different regions along the whole length of SEQ ID NO: 1. However, at the time of filing, the instant specification did not identify a single B-cell and/or T-cell protective epitope(s) within SEQ ID NO: 1 that is responsible for homologous or heterologous protection such that those of skill in the art would have known which regions within SEQ ID NO: 1 should be spared while producing at least 90% or at least 94% identical variant species within the claimed broad genus, without destroying the protective epitopes. Furthermore, the death of approximately 80% mice that were immunized with SEQ ID NO: 28 that comprises therein an amino acid sequence having as high as 99.8% sequence identity to SEQ ID NO: 1, when the immunized mice were challenged with one of the CL-10, CL-13 and CL-18 clinical isolates of *S. aureus* as demonstrated via Appellants' Figures 4A, 4D and 4G, provides additional evidence pointing to the lack of one or more B-cell and/or T-cell protective epitopes in the ORF0657nI-equivalent sequence of SEQ ID NO: 28. These are data from Appellants' own specification and are not based on the Office's speculations.

Clearly, the Office has established a *prima facie* case of lack of adequate written description by documenting the lack of possession of and the lack of sufficient structure-function correlation for a representative number of species encompassed within the very broad genus claimed.

Furthermore, the issue of unpredictability is very relevant to the instant rejection. It should be noted that written description requires more than a mere statement that something is a part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. The *Written Description Guidelines* state [Emphasis added]:

> … for inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species **cannot** be achieved by disclosing only one species within the genus.

Accordingly, an adequate written description of a highly varied genus cannot be achieved without the adequate description of a sufficient number of varied species representative of the full scope of the broad genus. The protective function of a representative number of the highly varied polypeptide immunogen species or the immunogen species encompassed within the claimed broad genus cannot be speculated, but must be correlated and concretely established as required under the written description provision of 35 U.S.C 112, first paragraph. In the instant case, possession of a sufficient number of varied species representing the huge genus has not been shown. The instant application does not provide an expectation that a representative number of polypeptide variant species covered by the full scope of the instant claims would be protective against *S. aureus.* This cannot be ignored given the art-recognized unpredictability associated with amino acid alterations within a polypeptide and given the Appellant-demonstrated unpredictability.

Appellants dismiss the teachings of Colman P.M. (*Research Immunol.* 145:33-36, 1994), McGuiness *et al.* (*Mol. Microbiol.* 7:505-514, Feb 1993), and McGuiness *et al.* (*Lancet* 337:514-517, March 1991) that were cited in the rejection as being very relevant to the issue of art-recognized unpredictability associated with one or more amino acid alterations within a polypeptide, and continue to allege that the Office has failed to provide sufficient rationale and evidence. The abundance of evidence provided by Appellants themselves within the instant application is sufficient to justify the lack of possession of and the lack of a concrete structure-function correlation for a representative number of species falling within the claimed vast genus, as well as justify the lack of predictability. The evidence of record is contrary to Appellants' argument that the ability of a polypeptide to provide protection against a heterologous strain of *S. aureus* demonstrates that alterations can be made to SEQ ID NO: 1 where protection is maintained and therefore provides a strong expectation that the corresponding region from the challenge strain could also provide protection.

The Office documents herein below the evidence from Appellants' own application that is directly indicative of the functional unpredictability of the numerous polypeptide variant species encompassed within the claimed broad genus:

Evidence number 1:

Particularly noteworthy in this regard are the mouse protection results obtained with two specific fragments of SEQ ID NO: 1 as illustrated via Figure 1A. Appellants' SEQ ID NO: 1 when modified with specific

known amino acid alterations by merely deleting amino acids 2-41 from its amino terminus, **did loose** its ability to provide protective immunity against a strain of *S. aureus*, despite retaining up to 91% sequence identity to SEQ ID NO: 1. The instant application at third full paragraph of page 8 states that a fragment of SEQ ID NO: 2 consisting of amino acids 82-486 and a fragment of SEQ ID NO: 2 consisting of 42-196 were **not protective**. See fragments 2 and 3 identified in Figure 1A and the brief description of the drawing for Figure 1A on page 5 of Appellants' specification. The amino acid residues 42-486 of SEQ ID NO: 2 constitute the full-length SEQ ID NO 1. The sequence consisting of the amino acids 82-486 of SEQ ID NO: 2 is fragment 2 of SEQ ID NO: 1 and has as high as 91% structural identity to SEQ ID NO: 1 and falls fully within the scope of claim 7 sequence identity-wise. This fragment 2 however has been definitively correlated by Appellants to the lack of protective function against *S. aureus*. See third full paragraph of page 8; fragment 2 in Figure 1A; and the brief description of the drawing for Figure 1A. Appellants have reemphasized this lack of protection by fragments of SEQ ID NO: 1 made up of amino acids 82-486, amino acids 42-196, and amino acids 461-609 of the full-length SEQ ID NO: 2 at second full paragraph on page 8 of their amendment/remarks filed 08/18/08. This Appellant-demonstrated showing cannot be ignored as 'some unidentified alteration' possibly impacting negatively on the ability of the altered SEQ ID NO: 1 to provide protection, but must be viewed as the *prima facie* demonstration of correlation of the structure of a polypeptide consisting of an amino acid sequence 91% identical to SEQ ID NO: 1 having specifically identified alterations therein, to the **lack** of protection

against *S. aureus*. This is indicative of the lack of strong expectation for SEQ ID NO: 1 having specifically identified alterations therein to remain protective against homologous or heterologous *S. aureus*. This provides further evidence for the lack of a single, let alone more than one, B-cell and/or T-cell protective epitopes within sufficiently lengthy fragments of SEQ ID NO: 1. Based on this Appellant-established correlation of the altered structure of SEQ ID NO: 1 to the lack of protection, one of skill in the art would not be able to predict 90%, 91%, 92%, 93%, 94%, 95%, 96%. 97%, 98% and 99.0% identical variants of SEQ ID NO: 1 to provide protective immunity against *S. aureus* in a human or non-human patient or subject. Furthermore, since the second fragment of SEQ ID NO: 1, fragment 3, covering the portions of SEQ ID NO: 1 not covered by fragment 2 plus the amino terminal portion of fragment 3, i.e., amino acids 2-154 of SEQ ID NO: 1, was also correlated by Appellants to **non-protection**, one of skill in the art cannot envision the specific location of one or more protective epitopes within SEQ ID NO: 1 that must be retained while obtaining 90%, 91%, 92%, 93%, 94%, 95%. 96%. 97%, 98% and 99.0% identical variants of SEQ ID NO: 1 that are protective. The fact that *the unmodified SEQ ID NO: 1 when merely split into a fragment of amino acids 82-486, or a fragment of amino acids 42-196, looses its protective capacity,* is indicative of the presence of potential conformational protective epitopes that require amino acid residues from different parts within SEQ ID NO: 1, which epitopes were neither identified by Appellants within the instant specification, nor were they known in the art at the time of the invention. This showing points to the criticality of retaining all the amino

acid residues except the N-terminal methionine of the SEQ ID NO: 1 core sequence intact within the claimed polypeptide fragment in order to retain the *requisite* function of providing protective immunity against *S. aureus*. If the result from Figure 1A for fragment 2 is to be extrapolated to a human patient, there would be no expectation of protection.

Evidence number 2:

The second evidence for unpredictability comes from Appellants' mouse experiment results obtained with SEQ ID NO: 4. SEQ ID NO: 4 is a polypeptide immunogen species that is 99.8% identical to an amino acid sequence consisting of SEQ ID NO: 1, with a single amino acid addition after its N-terminal methionine and having more than 20 additional amino acid moities at the carboxyl terminus of SEQ ID NO: 1. This SEQ ID NO: 4, when His-tagged at the carboxyl terminus, showed a statistically insignificant protection, compared to the protection induced by the AHP adjuvant alone in the control mice, against the Becker strain of *S. aureus* in an immune-sufficient mouse model, even though it was administered along with the AHP adjuvant. See Figure 3B. Despite its 99.8% identity to SEQ ID NO: 1, the SEQ ID NO: 4 polypeptide immunogen species provided almost the same percent survival as the one induced in the control mice by the AHP adjuvant alone. Such a species cannot and would not be considered by those of skill in the art as a polypeptide immunogen providing SEQ ID NO: 4-specific or SEQ ID NO: 1-specific protective immunity against heterologous *S. aureus*.

Evidence number 3:

The third evidence for unpredictability comes from Appellants' mouse experiment results obtained with the longer than full-length SEQ ID NO: 28.

The lengthy SEQ ID NO: 28 comprising therein a polypeptide that is 99.8% identical to SEQ ID NO: 1 with a single amino acid addition after the amino terminal methionine of SEQ ID NO: 1, upon administration to mice in an immune-sufficient mouse model of *S. aureus* infection, induced approximately 80% death (not 80% survival) of the animals immunized therewith, following a challenge infection with three different clinical isolates of *S. aureus,* CL-10, CL-13, or CL-18. See Figures 4A, 4D and 4G. The SEQ ID NO: 28 polypeptide showed a death rate almost equal to the one induced in control mice immunized with the AHP adjuvant alone. See Figure 4A. Such a species is not accepted by those of skill in the art as a polypeptide immunogen that provides protective immunity against multiple clinical isolates of heterologous *S. aureus*. If the approximately 80% death as seen from Appellants' Figures 4A, 4D and 4G for SEQ ID NO: 28 is to be extrapolated to a human patient, there would be no expectation of protection.

Evidence number 4:

An ORF0657nI sequence without any amino acid alterations showed no protection in BALB/C mice in the absence of the endotoxin adjuvant. Therefore, the issue of host species in which protective immunity against *S. aureus* is to be induced is very relevant to the unpredictability issue. Note that the generic limitation 'protective immunity against *S. aureus*' in claim 1 does not specify to whom the protective immune response is provided, and therefore broadly encompasses said response in any host species. Appellants' additional data made of record and the data from the specification concretely establish that the polypeptide immunogen species

falling within the scope of the claims were protective in one host species only when administered with the AHP or the endotoxin adjuvant. The additional data provided on 08/18/2008 documents that the ORF0657nI did not provide protection in BALB/C mice in the absence of the endotoxin adjuvant. See pages 7 and 8 of Applicants amendment/remarks filed 08/18/08. If this result is to be extrapolated to a human patient, including an immunesufficient, immunodeficient, immunosuppressed, and immunocompromised human patient, even the ORF0657nI sequence corresponding to the claimed polypeptide immunogen consisting of the recited amino acid sequence with no amino acid alterations, let alone its 94% or 90% identical variants, would be expected to be non-protective in human patients without an adjuvant. Note that the composition of claims 8 and 38-44 and the immunogen of claims 1, 4, 7, 33-35 and 49-51 do not contain an adjuvant and are still required to provide protective immunity against *S. aureus* in any host, or in a human and/or non-human patient.

Conclusion:

In sum, given the functional unpredictability documented within the instant application via the lack of protection by fragments 1-3, particularly the 91% identical ORF0657nI fragment 2, as illustrated via Figure 1A; given the demonstration of a statistically insignificant protection by SEQ ID NO: 4 against the Becker strain despite its 99.8% identity to SEQ ID NO: 1 as illustrated via Figure 3B; given the lack of protection correlated with an ORF0657nI with no amino acid alterations therein, in the absence of an adjuvant such as endotoxin as disclosed via the additional data provided by Appellants on pages 7 and 8 of their 'Remarks/Arguments' filed

08/18/2008; and given the death of approximately 80% of mice immunized with the His-tagged full-length SEQ ID NO: 28 comprising therein an amino acid sequence that is 99.8% identical to SEQ ID NO: 1 as illustrated via Figures 4A, 4D and 4G, one of skill in the art would not recognize that Applicants were in possession of a representative number of the *protective* polypeptide immunogen variant species or the *protective* immunogen variant species currently encompassed within the broad scope of the claims. In other words, a showing that an amino acid sequence 99.8% identical to SEQ ID NO: 1, which when comprised within the longer sequence of SEQ ID NO: 28 (a) kills approximately 80% of immunesufficient mice immunized with SEQ ID NO: 28 admixed with the AHP adjuvant following challenge infection with the CL-10, CL-13, or CL-18 clinical isolate of *S. aureus*; and (b) provides almost the same degree of mortality as induced in the control mice by the AHP adjuvant alone against CL-10 isolate of *S. aureus*; or (c) provides a moderate protection of approximately 40% against a laboratory strain of *S. aureus* compared to the 20% protection conferred by the AHP adjuvant alone, is insufficient to show possession of the huge genus of polypeptide variants or immunogen variants of the recited percent sequence identity as claimed. With the above-identified lack of structure-protective function correlation as demonstrated within Appellants' specification, the ability of the corresponding ORF0657nI or ORF0657nH region from CL-10, CL-13, CL-30, CL-18 and CL-21 to provide protection against any strain of *S. aureus,* is simply not predictable. 'A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a

single species when … the evidence indicates that ordinary artisans could not predict the operability in the invention of any species other than the one disclosed'. *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004). See MPEP 2163 IBII.A.

If one lifted or isolated the SEQ ID NO: 1-equivalent region from each sequence depicted in Figures 2A-2E and evaluated it for protection against homologous or heterologous *S. aureus* in an immune-sufficient or immune-deficient animal model, there is a great likelihood that one of skill in the art would observe a lack of protection as observed with fragment 2 having 91% identity to SEQ ID NO: 1, or would observe the death of approximately 80% of immunized mice upon challenge as seen with the longer polypeptide comprising an amino acid sequence that is 99.8% identical to SEQ ID NO: 1. Since none of the tested SEQ ID NO: 3, 4 and 5 have been correlated with homologous protection, the ability of the corresponding ORF0657nI or ORF0657nH region from CL-10, CL-13, CL-30, CL-18 and CL 21 to provide protection against the homologous strain is not predictable. Given that the structure of fragment 2 polypeptide having 91% identity to SEQ ID NO: 1 and fragment 3 covering the rest of the length within SEQ ID NO: 1 has been definitively correlated within the instant specification with lack of protection and given that the structure of a longer polypeptide comprising therein an amino acid sequence that is 99.8% identical to SEQ ID NO: 1 has been correlated with approximately 80% death of the immunized mice upon challenge with diverse clinical isolates of *S. aureus*, there is no predictability that one of skill in the art would be able to correlate the disclosed structure of the ORF0657nI-

equivalent region of the full-length sequences from Figures 2A-2E, with protection against homologous or heterologous *S. aureus* in an animal, let alone a human patient or subject.

The Office's *prima facie* case of lack of adequate written description rejection should be sustained as it is fully supported by the combined showing of the lack of possession of a sufficient number of species representative of the claimed broad genus, the lack of structure-function correlation for a representative number of species encompassed within the claimed broad genus, and the Appellant-demonstrated unpredictability and lack of expectation of protection.

(II) In response to the rejection of claim 7 made in paragraph 25(g) of the Office Action mailed 11/24/09 and maintained in paragraph 17 of the Office Action mailed 03/25/10 under 35 U.S.C § 112, second paragraph, as being indefinite, Appellants submit the following **arguments**.

Appellants reproduce the amended claim 7 and state that the reference to "facilitates polypeptide stability" in claim 7 clearly refers to a property of the additional region or moiety, where the additional region or moiety is joined to said sequence. Applicants contend that properties of additional regions or moieties are listed in a Markush group and that one of the indicated properties is facilitates polypeptide stability.

The Office submits the following **response** to Appellants' arguments:

Appellants' arguments do not address the indefiniteness issue of record. Whether or not the additional region or moiety is joined to the recited sequence is not the basis of the rejection. The indefiniteness issue

was raised with regard to the limitation 'facilitates polypeptide stability', because it is unclear the stability of *which polypeptide* is being facilitated by the one or more additional regions or moieties, since the earlier parts of the claim do not refer to any 'polypeptide'. Appellants do not address this issue. The relationship, if any, of the polypeptide whose stability is facilitated to the claimed immunogen remains unclear and not understood.

For the reasons delineated above, the rejection should be sustained.

(III) In response to the rejection of claim 8 made in paragraph 25(f) of the Office Action mailed 11/24/09 and maintained in paragraph 16 of the Office Action mailed 03/25/10 under 35 U.S.C § 112, second paragraph, as being indefinite, Appellants submit the following **arguments**.

Appellants cite case law and state that definiteness under 35 U.S.C. 112, second paragraph, is determined based on whether those skilled in the art would understand what is claimed when the claim is read in light of the specification. Appellants contend that claim 8 is a composition claim, not a method of use claim. Appellants state that the preamble description of a patient indicates a possible use of the composition and is not a limitation *necessitating* the use of the immunogen in a patient. Appellants argue that reference to providing protective immunity against *S. aureus* in the body of the claim refers to a property of the composition consistent with the claim preamble and that the body of the claim also refers to a pharmaceutically acceptable carrier as part of the composition. Appellants assert that the skilled artisan reviewing the specification would readily understand that when the composition is used, the production of an

immune response is to occur in the patient in which the immunogen is administered. Appellants state that the application on page 7, line 34 to page 8, line 1, mentions protective immunity using an animal model and the examples described in the application illustrate an immune response in an animal model to which the immunogen was added. Appellants state that the Office's position that the claims cover a composition that when administered to one patient, produces an effect in a second patient, is contrary to the present application and the plain wording of the claim.

The Office submits the following **response** to Appellants' arguments:

Claim 8, as amended, is vague and indefinite in the broadening limitation: 'provides protective immunity against *S. aureus*' in line 3. The earlier part of the claim includes a narrower limitation reciting that the composition is to induce a protective immune response against *S. aureus* 'in a patient'. The earlier narrower limitation: 'composition *able to induce a protective immune response against S. aureus in a patient'* comprising an *immunologically effective amount of* a purified polypeptide immunogen, is presented with the latter broader limitation '*that provides protective immunity against S. aureus*', which renders the claim indefinite. The latter limitation 'immunologically effective amount …… that provides protective immunity against *S. aureus'* does not recite --said protective immunity-- and does not specify that the immunologically effective amount that provide protective immunity against *S. aureus* is --in said patient--, and therefore encompasses an immunologically effective amount of a purified immunogen that provides protective immunity against *S. aureus* in a non-

patient, or a patient other than the one recited in line 2 of the claim. It is unclear, whether the immunologically effective amount of the recited purified polypeptide immunogen that provides protective immunity against *S. aureus* (for example in ICR mice) as recited in line 3 of the claim is the amount of the purified polypeptide immunogen that provides protection against the same or a different strain of *S. aureus* in a patient recited in line 2 (for example a patient BALB/c mouse). When claim 8 is read in light of what Appellants have made of record in the instant application, one would note Appellants' documentation of 'variability in whether or not protection is seen depending upon the model used to evaluate protection', and the indication that an amount immunologically effective in ICR mice cannot be or may not be an amount that is immunologically effective in BALB/c mice patient. See the section 'Additional Data' on page 7 of Applicants' amendment filed 08/18/2008. Claim 8 continues to be indefinite.

For the reasons delineated above, the rejection should be sustained.

(IV) In response to the rejection of claims 9 and 38-54 made in paragraph 25(i) of the Office Action mailed 11/24/09 and maintained in paragraph 18 of the Office Action mailed 03/25/10 under 35 U.S.C § 112, second paragraph, as being indefinite, Appellants submit the following **argument**.

Appellants contend that claim 8 and claim 7, from which instant claims depend, are not indefinite.

However, as explained *supra*, claims 7 and 8 are indefinite, and therefore the dependent claims 9 and 38-54 are also indefinite.

For the reason delineated above, the rejection should be sustained.

(12) Related Proceedings Appendix

No decision rendered by a court or the Board is identified by the Examiner in the Related Appeals and Interferences section of this examiner's answer.

Respectfully submitted,

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